Synthetic and mechanistic studies involving selected bridged polycyclic compounds.

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SYNTHETIC AND MECHANISTIC STUDIES

INVOLVING SELECTED BRIDGED POLYCYCLIC COMPOUNDS

A Thesis presented for the Degree of
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by

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This thesis is dedicated to my parents.

ABSTRACT

The iodolactonisation of 3-exo-methylnorborn-5-en-2-endo-ylacetic acid and 3-exo-phenylnorborn-5-en-2-endo-ylacetic acid afford 6-endo-hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylacetic acid δ-lactone and 6-endo-hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo-ylacetic acid δ-lactone respectively, in both of which the lactone ring has a chair conformation.

The iodolactonisation of norborn-5-en-2-endo-ylpropionic acid and norborn-5-en-2-endo-ylbutyric acid does not follow the same pattern, and instead the rearrangement products 3'-(2-exo-hydroxy-7-anti-iodonorborn-2-endo-yl)propionic acid spiro-γ-lactone and 4'-(2-exo-hydroxy-7-anti-iodonorborn-2-endo-yl)butyric acid spiro-δ-lactone respectively are obtained.

Acid catalysed cyclisation of norborn-5-en-2-yl-propionic acid and norborn-5-en-2-ylbutyric acid does follow a pattern similar to their iodolactonisation reactions and gives the respective 3'-(2-exo-hydroxynorborn-2-endo-yl) propionic acid spiro-γ-lactone and 4'-(2-exo-hydroxynorborn-2-endo-yl)butyric acid spiro-δ-lactone.

6-endo-Hydroxy-5-exo-iodonorborn-2-endo-ylcarboxylic acid γ-lactone with silver tosylate affords 7-syn-hydroxy-3-exo-tosyloxynorborn-6-exo-ylcarboxylic acid γ-lactone as the sole product. The comparable reaction with 6-endo-hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylcarboxylic acid γ-lactone and 6-endo-hydroxy-5-exo-iodo-3-exo-

phenylnorborn-2-endo-ylcarboxylic acid γ-lactone gives a mixture of 7-syn-hydroxy-5-endo-methyl-3-exo-tosyloxynorborn-6-exo-ylcarboxylic acid γ-lactone and 6-endo-hydroxy-3-exo-methylnorborn-2-endo-ylcarboxylic acid γ-lactone, and a mixture of 7-syn-hydroxy-5-endo-phenyl-3-exo-tosyloxy-norborn-6-exo-ylcarboxylic acid γ-lactone,6-endo-hydroxy-3-exo-phenyl-5-exo-tosyloxynorborn-2-endo-ylcarboxylic acid γ-lactone and α-(cis-2-hydroxycyclopent-3-en-1-yl)-E-cinnamic acid γ-lactone respectively.

6-endo-Hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylacetic acid δ-lactone and 6-endo-hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo -ylacetic acid δ-lactone on the same treatment with silver tosylate in addition to the products anticipated on the basis of the results with 6-endo-hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylcarboxylic acid γ-lactone also afford 6-endo-hydroxy-3-methylenenorborn-2-endo-ylacetic acid δ-lactone and 7-anti-hydroxy-5-endo-phenylnorborn-2-en-6-exo-ylacetic acid δ-lactone respectively.

A study was made into the preparation of 5-(4'β-hydroxymethyl-2'β, 3'β-dihydroxycyclopent-1'β-yl)6-azauracil. 3-Carbomethoxy-5-endo, 6-endo-O-isopropylidene-norborn-2-ene, the required intermediate for this synthesis is obtained from 5-endo, 6-endo-dihydroxynorborn-2-endo, 3-endo-yldicarboxylic acid bis-γ-lactone.

An approach to the synthesis of 2-carbomethoxy-5-endo, 6-endo-O-isopropylidene-7-oxa-bicyclo [2.2.1.] hept-2-ene from Diels-Alder adduct of furan with fumaryl chloride was also carried out.

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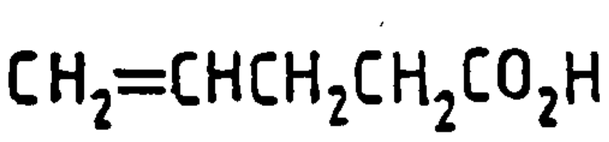
1.0.0.0. CHAPTER 1. INTRODUCTION.

1.1.0.0. Lactonisation of unsaturated acids.

1.1.1.0. Iodolactonisation.

1.1.1.1. General Introduction.

Bougault[1-4] was the first to show that β, γ and γ, δ-unsaturated acids may be converted into iodolactones. The standard procedure was to treat a solution of the acid in aqueous sodium bicarbonate with a solution of iodine in aqueous potassium iodide.



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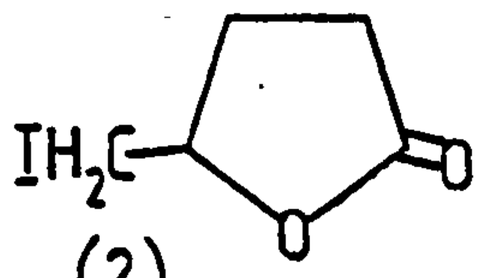

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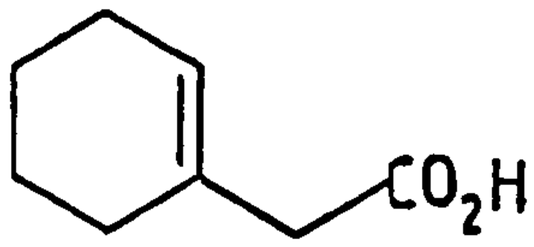

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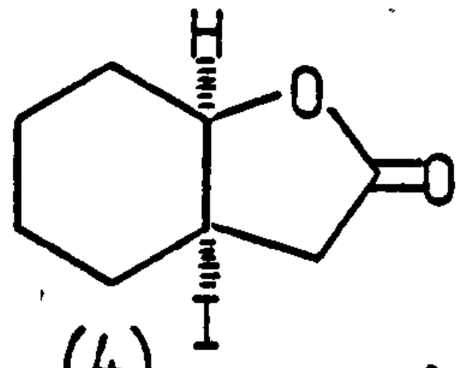

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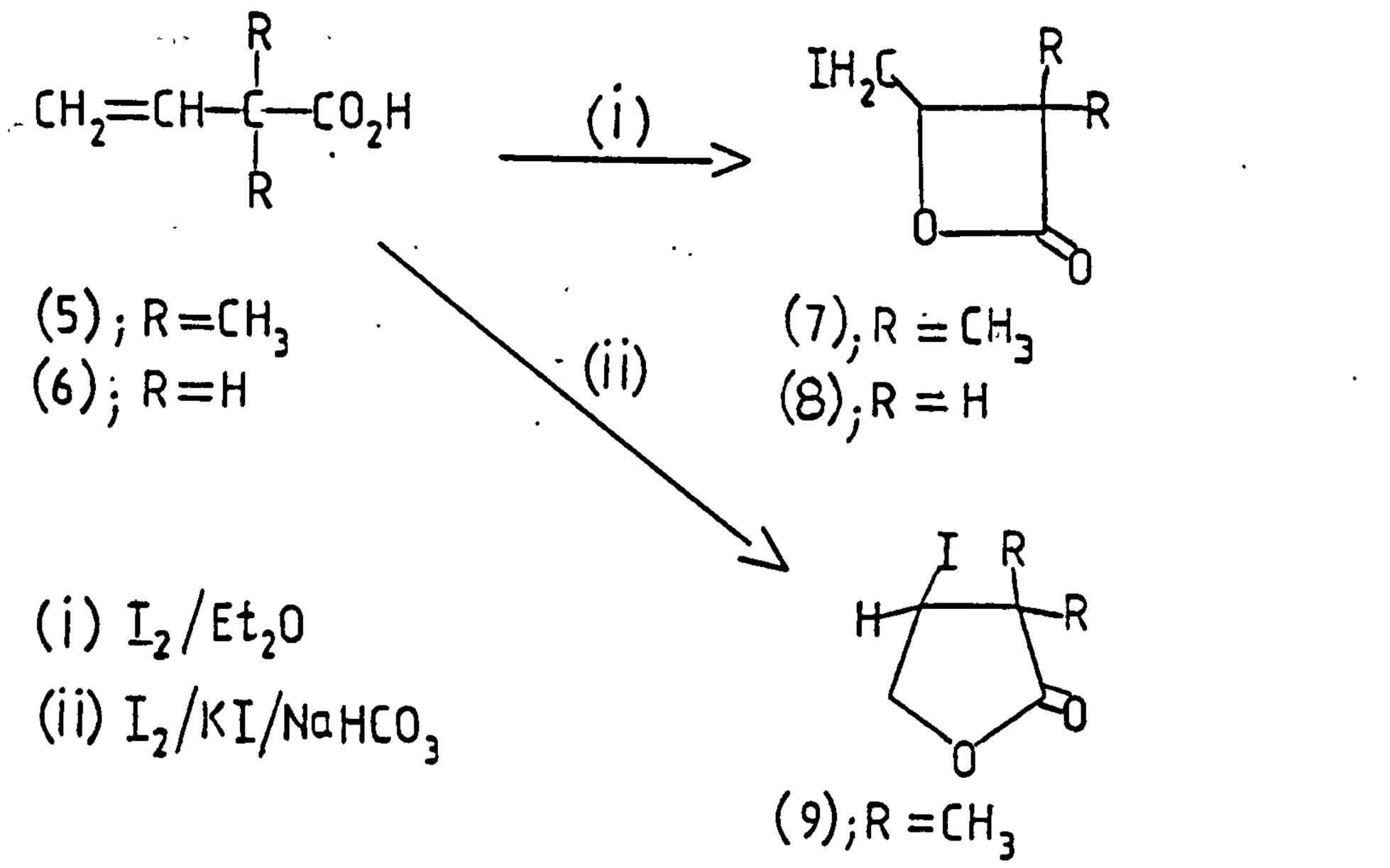
Illustrative of iodolactonisation is the conversion of γ,δ-pentenoic acid (1)[5,6] and cyclohex-1-en-1-ylacetic acid (3)[5,7,8] into the respective γ-lactones (2) and (4).

1.1.1.2. Reagents and reaction conditions.

Reactions are usually carried out in aqueous media although organic solvents such as chloroform[6,9] and carbon tetrachloride,[10] and mixed solvents such as tetrahydrofuran/water[11] and saturated aqueous sodium

bicarbonate/ether[12,13] have been used. Temperatures between 0^{o} and 80^{o} are usually employed and reaction times vary from several minutes to three days. Barnett[12,13] found that with long reaction times treatment of β,γ-unsaturated acids with iodine in aqueous potassium iodide invariably afforded γ-lactones but with shorter reaction times in the presence of an organic solvent iodo-β-lactones sometimes resulted. Thus 2,2-dimethylbut-3-enoic acid (5) and but-3-enoic-acid (vinylacetic acid) (6) gave the respective iodo-β-lactones (7) and (8) with short reaction times using ether as solvent in the absence of potassium iodide. Under the standard conditions, the acid (5) gave the iodolactone (9) but the acid (6) did not react.



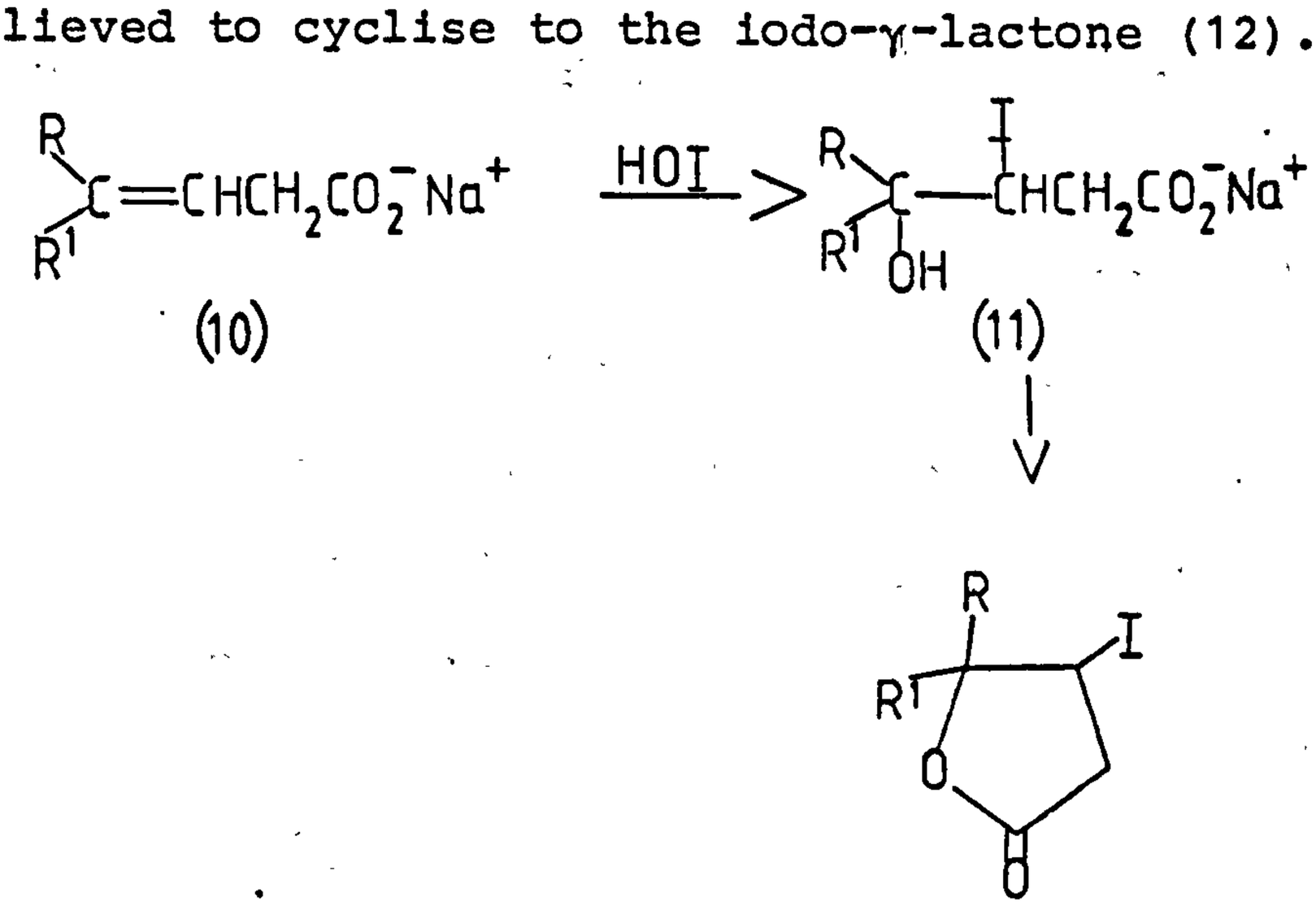
It would appear that iodo-β-lactones are the kinetically favoured and iodo-γ-lactones the thermodynamically favoured products.

Bougault's initial work indicated that α,β-unsaturated acids did not react to give iodo-β-lactones under the conditions

of the standard procedure. Indeed, because of this, the procedure could be used to separate α,β-unsaturated acids from β,γ- and γ,δ-unsaturated acids since only the latter two types of acid would form iodolactones. Later Ponzio and Gastaldi[14] found however that α,β- unsaturated acids would form iodo-β-lactones but a prolonged reaction time was needed.

1.1.1.3. <u>General mechanism and stereochemistry</u>.

Bougault thought the mechanism for iodolactonisation involved the initial formation of an iodohydrin, such as (11) by the addition of hypoiodous acid to the double bond of the unsaturated acid (10). Subsequently (11) was believed to cyclise to the iodo-γ-lactone (12).

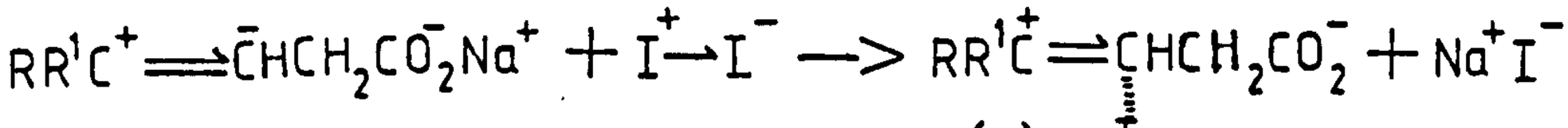


(10) (11)

(12)

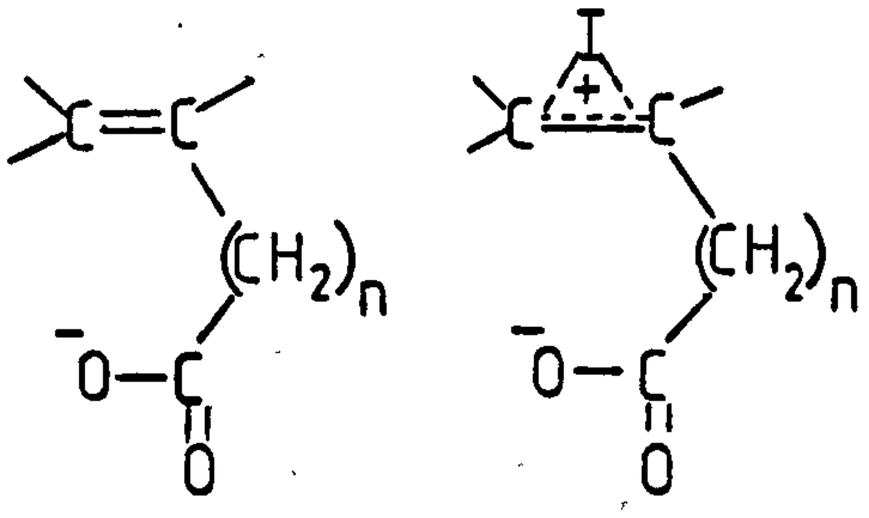
Subsequent work by Linstead and May[8] established the importance of the attack of positive iodine to the negatively polarised carbon of the double bond in the unsaturated acid (10) and suggested that an iodozwitterion (13)

was formed which then cyclised to give the iodolactone (12).



(10) (13) (12)

The currently accepted mechanism due to van Tamelen and Shamma[5] is outlined below;



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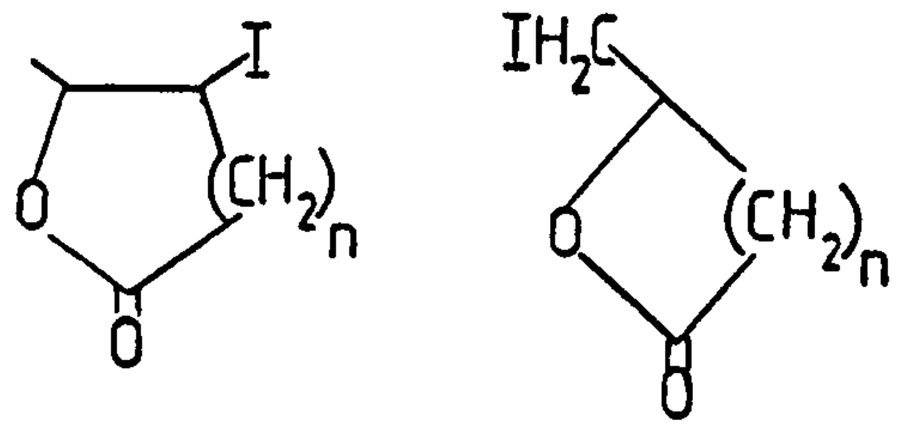
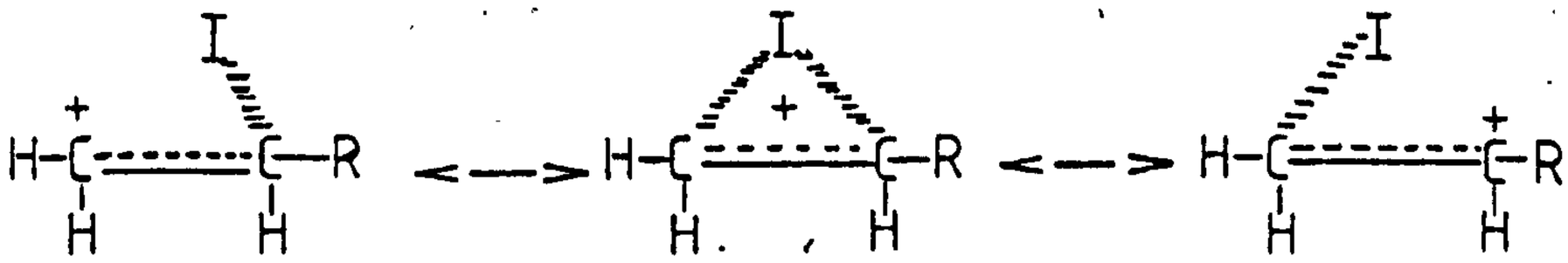


(16) (17)

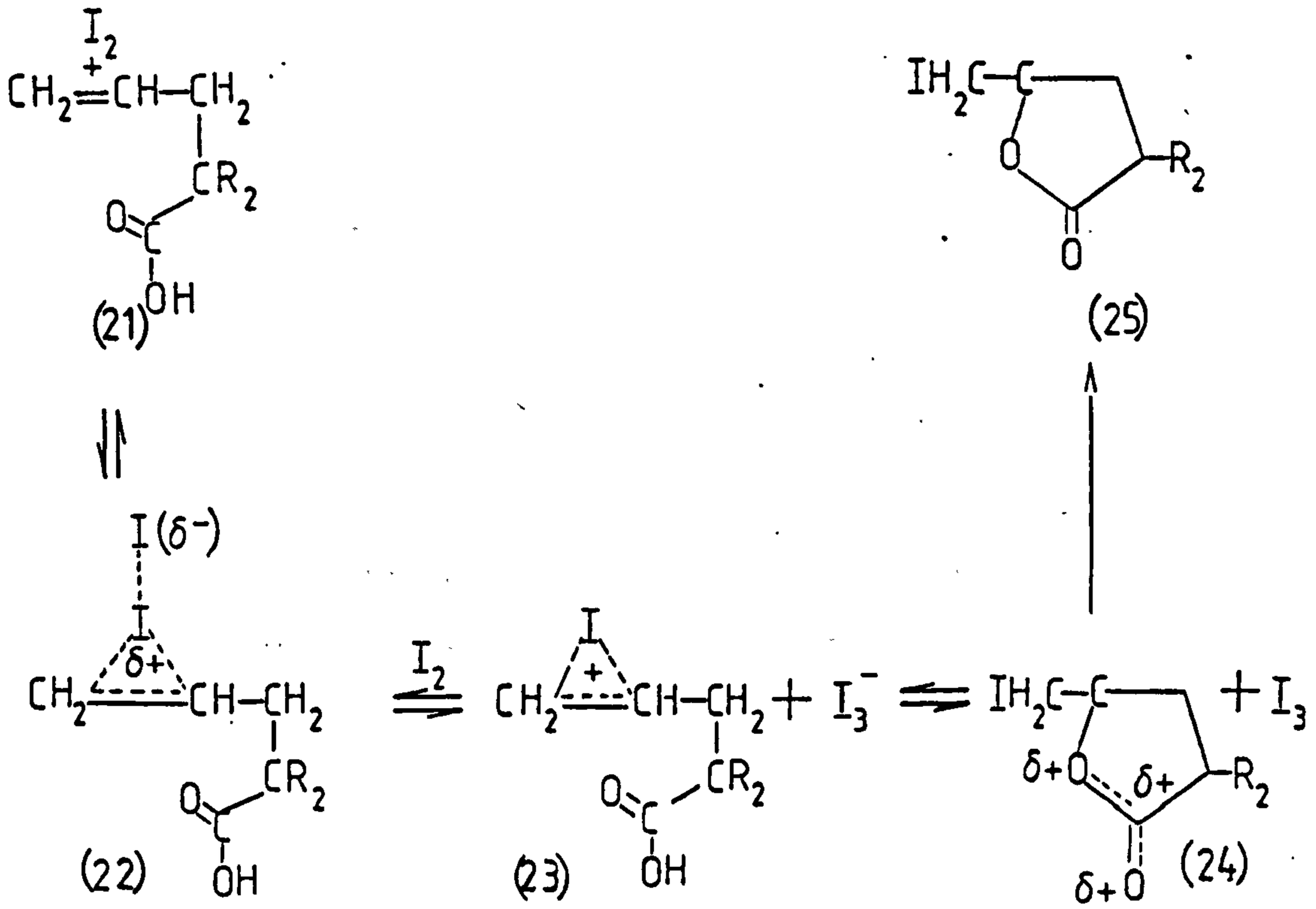
Attack of positive iodine on the double bond of the unsaturated carboxylate anion (14) gives (15) in which the carboxylate anion centre cyclises onto the iodonium ion centre to afford product (16) or (17). The reaction is controlled by electronic and stereochemical factors. The iodonium ion (19), R = $(CH_2)_nCO_2^-$ is believed to be the intermediate rather than the open carbonium ions (18) and (20). Thus vinylacetic acid (n = 1) is relatively inert since the canonical form (18) which logically leads to γ-lactonisation is a primary carbonium ion and contributes less than (20) to the hybrid (19).



(18) (19) (20)

Successful iodolactonisation generally involves a secondary carbonium ion either γ- or δ- to the carboxylate anion. Substituents on carbon α- to the carboxylate anion appear to promote reaction and this was explained by Berti[15] on the basis of a buttressing effect. This would bring the cationic intermediate and carboxylate anion into a sufficiently close proximity for them to enter into a transition state for lactonisation and prevent scavenging of the cation by iodine.

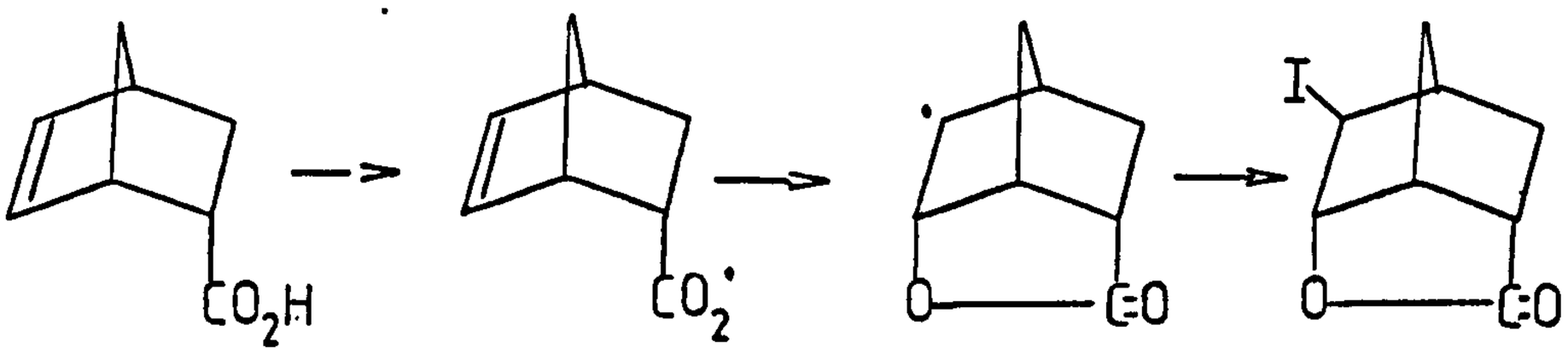
In non-polar solvents e.g. chloroform, Amaral and Melo[16] proposed the following mechanism for the iodo-lactonisation of γ,δ- unsaturated acids.



An initial complex (22) formed from a mole of iodine and the acid reacts with a second mole of iodine to give triiodide ion I_3^- and the intermediate iodonium ion (23), in which the positive charge is dispersed; this is followed by intramolecular cyclisation in (23) to give

the iodo-γ-lactone (25).

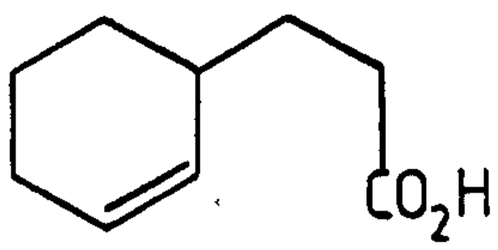
In the Cristol-Firth modification of the Hunsdiecker reaction,[10,17] a carboxylic acid on treatment with iodine and mercuric oxide is converted into an alkyl iodide. This procedure with unsaturated acids can afford iodolactones, and has been applied particularly to norbornene-2-endo-ylcarboxylic acid (26).[10]



(26) (27) (28) (29)

An initially formed carboxylate radical (27), cyclises to give (28) which affords the iodo-γ-lactone (29) by abstraction of an iodine atom from the iodine molecule.

Iodolactonisation generally proceeds preferentially to give cis-fused lactones, even though other modes of reaction do not appear to be prohibited on steric grounds.[18] For example cyclohexenylpropionic acid (30) affords a single cis-fused iodolactone (31) and none of either the cis-fused lactone (32) or trans-fused lactone (33).



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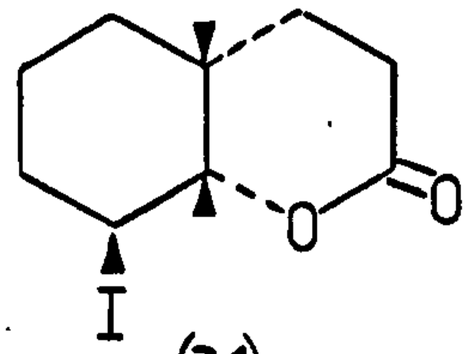

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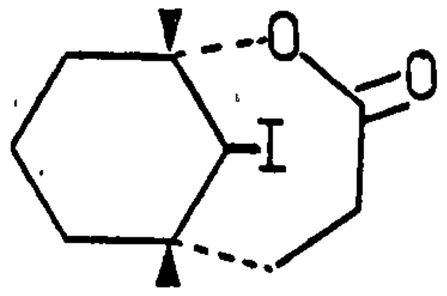

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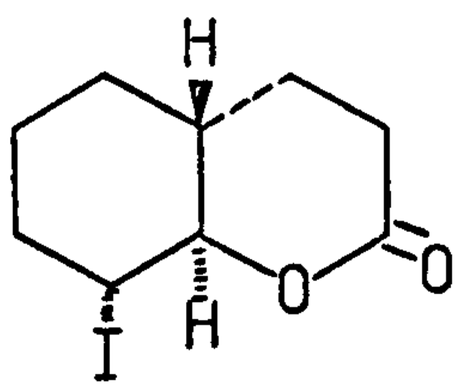

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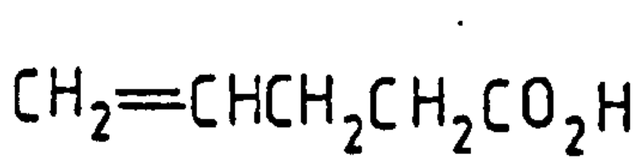
1.1.2.0. <u>Acid catalysed lactonisation</u>.

1.1.2.1. <u>General introduction</u> .

Fittig[19-22] first reported the acid catalysed lactonisation of unsaturated acids. The procedure was to heat under reflux a boiling solution of an α,β-,β,γ- or γ,δ- unsaturated acid in 50% aqueous sulphuric acid; the corresponding γ- or δ- lactone was obtained from the β,γ- and γ,δ- unsaturated acids respectively while the α,β- unsaturated acid was unchanged.

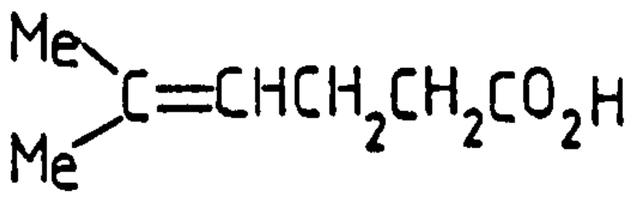


(1)

As an illustrative example is the conversion of the γ,δ- pentenoic acid (1)[23] into the γ-lactone (34).

1.1.2.2. Reagents and reaction conditions.

The reactions have been carried out in aqueous media mostly using sulphuric acid although in some cases toluene-p-sulphonic acid,[24] formic acid,[25] oxalic acid,[26] trifluoroacetic acid,[27] hydrogen fluoride[28] and hydrogen halides in acetic acid[28,29] have been used. Reaction temperature tend to vary from room temperature to 150° and the reaction time from several minutes to 48 hr.



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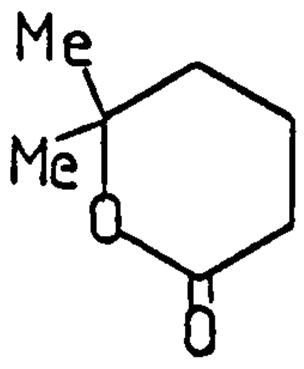

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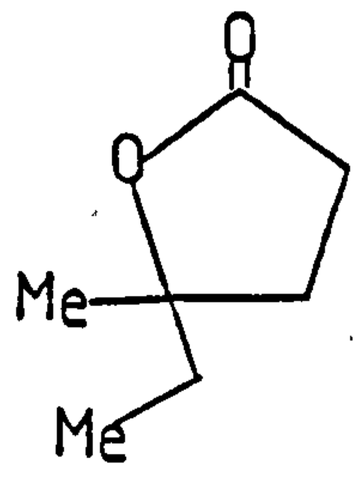
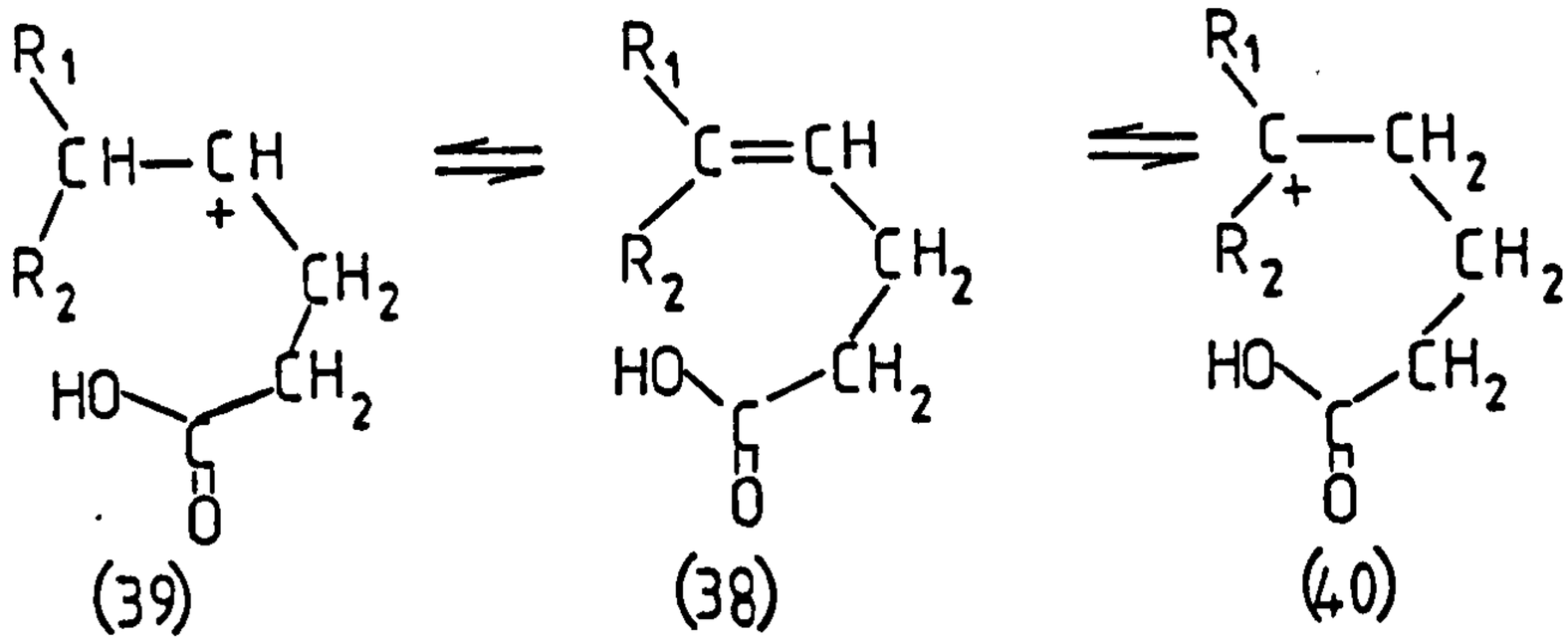


(37)

Ansell and Palmer[29] reported that for certain unsaturated acids the structure of the product lactone was dependent on the temperature and the reaction time. Thus5,5-dimethylpent-4-enoic acid (35) with cold concentrated sulphuric acid gave the δ-lactone (36) but when boiled with 50% aqueous sulphuric acid the γ-lactone (37) resulted.

1.1.2.3. Mechanism and stereochemistry.

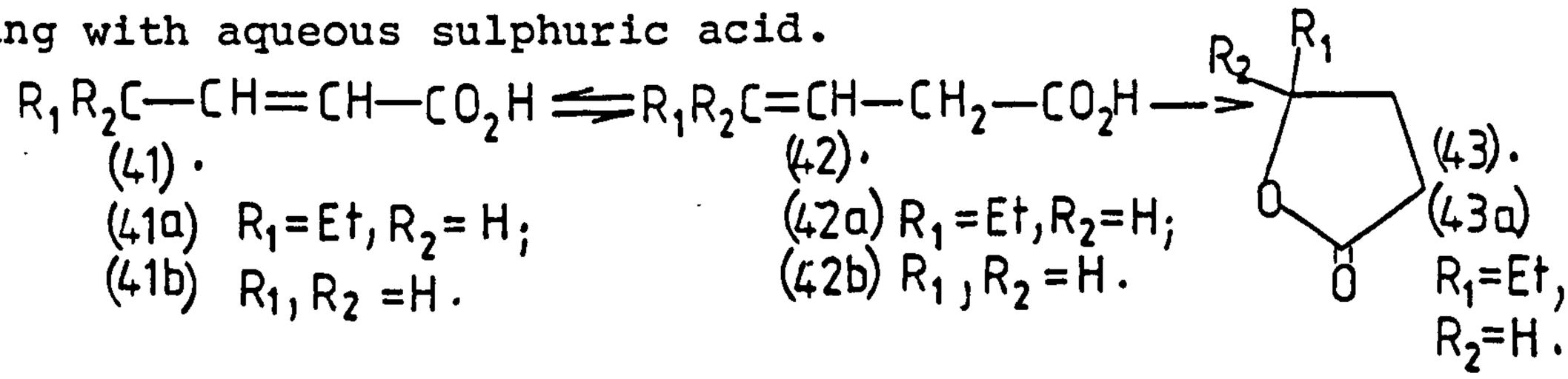
Linstead and Rydon[23] suggested that γ,δ-unsaturated acids would undergo acid catalysed lactonisation in two directions with the formation of either a γ- or a δ-lactone dependent on the stability of the intermediate carbonium ions (39) and (40).



(39) (38) (40)

The presence of the alkyl groups R_1, R_2 would determine whether the intermediate which leads to the stable lactone formation is either a primary, secondary or tertiary carbonium ion. Thus the γ-lactone (34) and not the δ-lactone resulted from the γ,δ- pentenoic acid (1) because of the stability of intermediate (39) compared to the intermediate (40); R_1,R_2 = H. In contrast the δ- lactone (36) is formed through the tertiary carbonium ion intermediate (40); R_1, R_2 = Me from the5,5-dimethylpent-4-enoic acid (35).

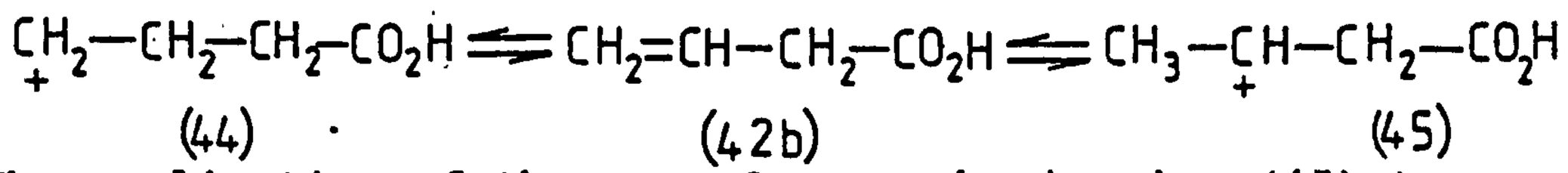
The effect of the substituents could clearly also be seen during formation of a γ-lactone (43) from the α,β- unsaturated acid (41)[30] which resulted from the isomerisation to the β,γ- unsaturated acid (42) on heating with aqueous sulphuric acid.



(41). (42). (43).
(41a) R_1=Et, R_2= H; (42a) R_1=Et, R_2=H; (43a) R_1=Et, R_2=H.
(41b) R_1, R_2 =H. (42b) R_1, R_2 =H.

Thus hex-2-enoic acid (41a) is isomerised to hex-3-enoic acid (42a) and cyclised to afford the γ-lactone (43a). The inertness of the vinylacetic acid (42b)

toward cyclisation was explained by Boorman[31] because it was isomerised to the more stable but-2-enoic acid (41b) or in terms of carbonium ion, the resulting primary carbonium ion (44), which logically would form a γ-lactone, is less reactive as earlier described by van Tamelen and Shamma[5] during iodolactonisation.



(44) (42b) (45)

The cyclisation of the secondary carbonium ion (45) to a β- lactone is less favoured because of the steric effect, and generally successful cyclisation involves a secondary carbonium ion either γ-or δ- to the carboxylate anion.

1.2.0.0. Reaction of alkyl halides with silver salts.

1.2.1.0. Reagents and reaction conditions.

A variety of silver salts such as silver nitrite,[32,51-53] silver nitrate,[33-43] silver perchlorate,[44] silver acetate,[45-46] silver cyanide,[47] silver carbonate,[48] and silver tosylate[49,50,54] have been found to react with alkyl halides. The reactions have mostly been carried out in acetonitrile because of the higher solubility of certain silver salts such as silver tosylate, silver nitrite and silver nitrate in the solvent at room temperature. Other solvents like benzene,[51] cyclohexane,[51] light petroleum[51] and diethyl ether[61] have also been used, and the reaction temperatures varied between -35^{o} to 110^{o}.

1.2.1.1. Meyer and Stuber[32] first reported a reaction involving silver salts and alkyl halides. They heated isoamyl iodide and silver nitrite at reflux to afford isoamyl nitrite and the corresponding nitro compound. The reaction was claimed to be of general applicability and could be written as below:

$$RX + AgNO_2 \longrightarrow RNO_2 + RONO\ ;\ X = I, Br, Cl.$$

The reactions temperature can affect the product formation;[51] as an example reaction of silver nitrite with 2-bromo-octane at 80^{o} to 110^{o} besides giving the corresponding 2-nitrooctane and 2-octyl nitrite also afforded side products such as 2-octyl nitrate, 2-octanol, 2-octanone together with other unidentified products.

The formation of the 2-octyl nitrate was believed to be due to the thermal instability of silver nitrite which decomposed at 80^{o} or above to silver nitrate which then reacted with the 2-bromooctane.

$$2\ AgNO_2 \longrightarrow AgNO_3 + Ag + NO$$

$$AgNO_3 + CH_3(CH_2)_5CH(Br)CH_3 \longrightarrow CH_3(CH_2)_5CH(ONO_2)CH_3 + AgBr$$

Primary bromides and iodides with silver nitrite were found to give better yields of primary nitro compounds when allowed to react initially at 0^{o} and subsequently at room temperature[52] to complete reaction. Thus 1-bromo-octane and 1-iodoheptane yielded 1-nitrooctane (80%) and 1-nitroheptane (82%) respectively; the corresponding primary chlorides were unchanged under those conditions.

Secondary halides[53] gave (∿15%) yield of nitro compounds in a temperature range from 0^{o} to 25^{o} with increased formation of nitrite esters and olefin derived from the dehydrohalogenation of the alkyl halides.

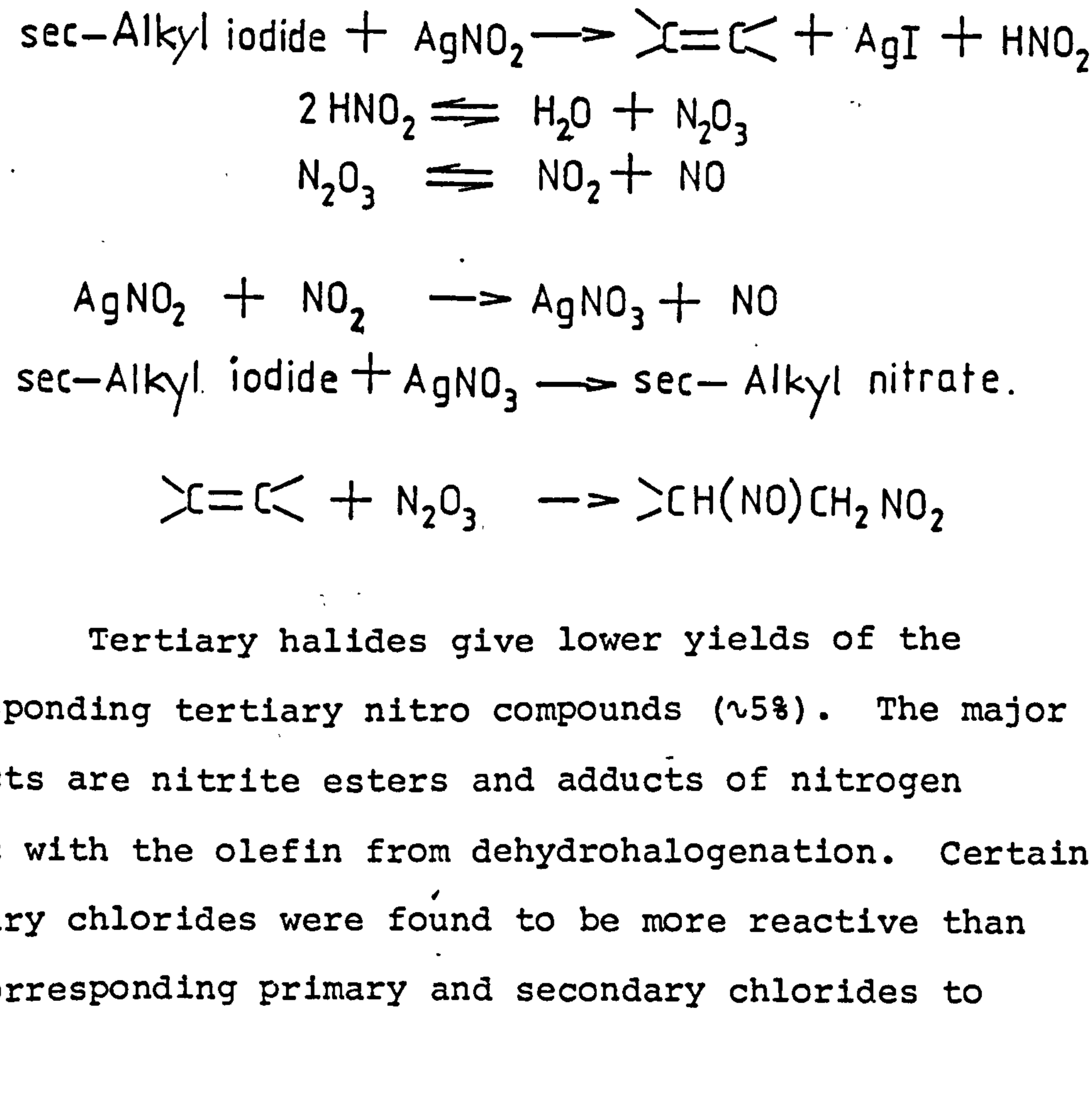
Two additional side reactions occurred as a result of the dehydrohalogenation processes:

(a) The "low temperature" formation of nitrate esters.

(b) Unspecified products formed by the addition of oxides of nitrogen to the olefin.

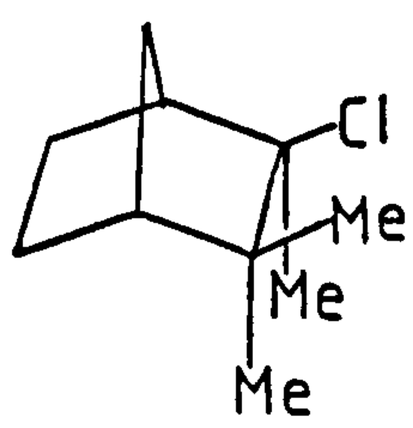
The formation of nitrate esters and the adduct of nitrogen oxides to the olefin is outlined in Scheme 1:

Scheme 1

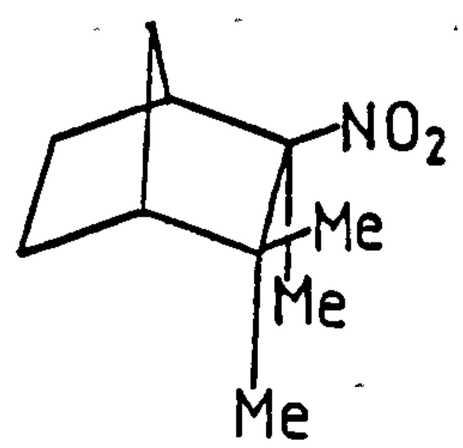


Tertiary halides give lower yields of the corresponding tertiary nitro compounds (∿5%). The major products are nitrite esters and adducts of nitrogen oxides with the olefin from dehydrohalogenation. Certain tertiary chlorides were found to be more reactive than the corresponding primary and secondary chlorides to

afford nitro compounds. As an example Stein[55] found the nitro compound (46) was obtained from camphene hydrochloride (45).



(45)



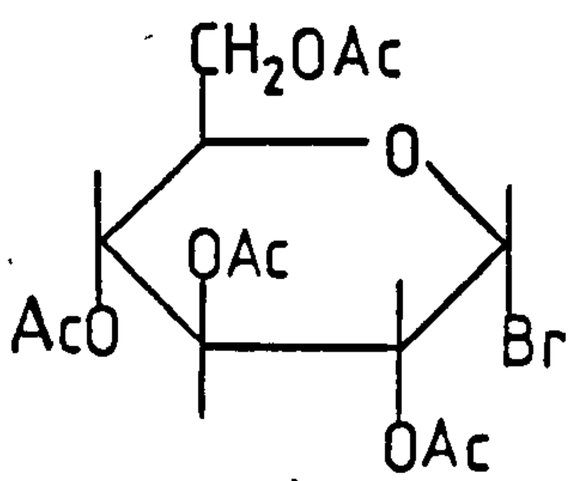
(46)

1.2.2.2. The procedure of Suter[56] for the preparation of alkyl sulphonates by heating silver sulphonate with an alkyl iodide was generally limited by the heterogenous reaction conditions and the relatively high temperature to effect complete reaction. The reaction was improved by Emmons and Ferris[49] by using acetonitrile as a solvent. The higher solubility of the silver salts of methanesulphonic acid, p-toluenesulphonic acid and benzenesulphonic acid resulted in a homogenous reaction medium and higher yields of alkyl sulphonates from primary alkyl halides. Thus methyl iodide gave methyl mesylate (97%) from silver methanesulphonate, methyl tosylate (77%) from silver tosylate and methyl benzenesulphonate (69%) from silver benzenesulphonate. Secondary and tertiary halides afforded only dehydrohalogenation products consistent with an earlier observation of the reaction of alkyl halides with silver nitrite.

Hoffmann[50] found out that the dehydrohalogenation product mentioned earlier by Emmon and Ferris could be

appreciably reduced by carrying out the reaction at -35^{o} and in this way Hoffmann successfully prepared unstable tosylates from secondary and tertiary alkyl halides such as t-butyl tosylate, diphenylmethyl tosylate and 1-phenylethyl tosylate. The versatility of the reaction of silver tosylate was also reported by Kornblum[54] who prepared the tosylates from certain primary benzylic and long chain aliphatic halides, which he then found could be readily oxidised to the corresponding aldehyde with a mixture of sodium bicarbonate and dimethyl sulphoxide. For example n-heptanaldehyde in 70% yield was obtained from heptyl tosylate which was prepared from 1-iodoheptane and silver tosylate.

1.2.2.3. Certain silver salts are also useful reagents in sugar chemistry e.g. silver carbonate[48] in the conversion of acetobromoglucose (47) to β-D-glucose-2,3,4,6-tetraacetate (48).



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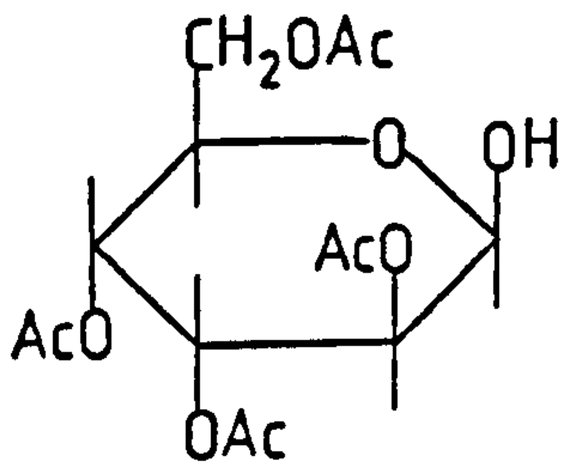
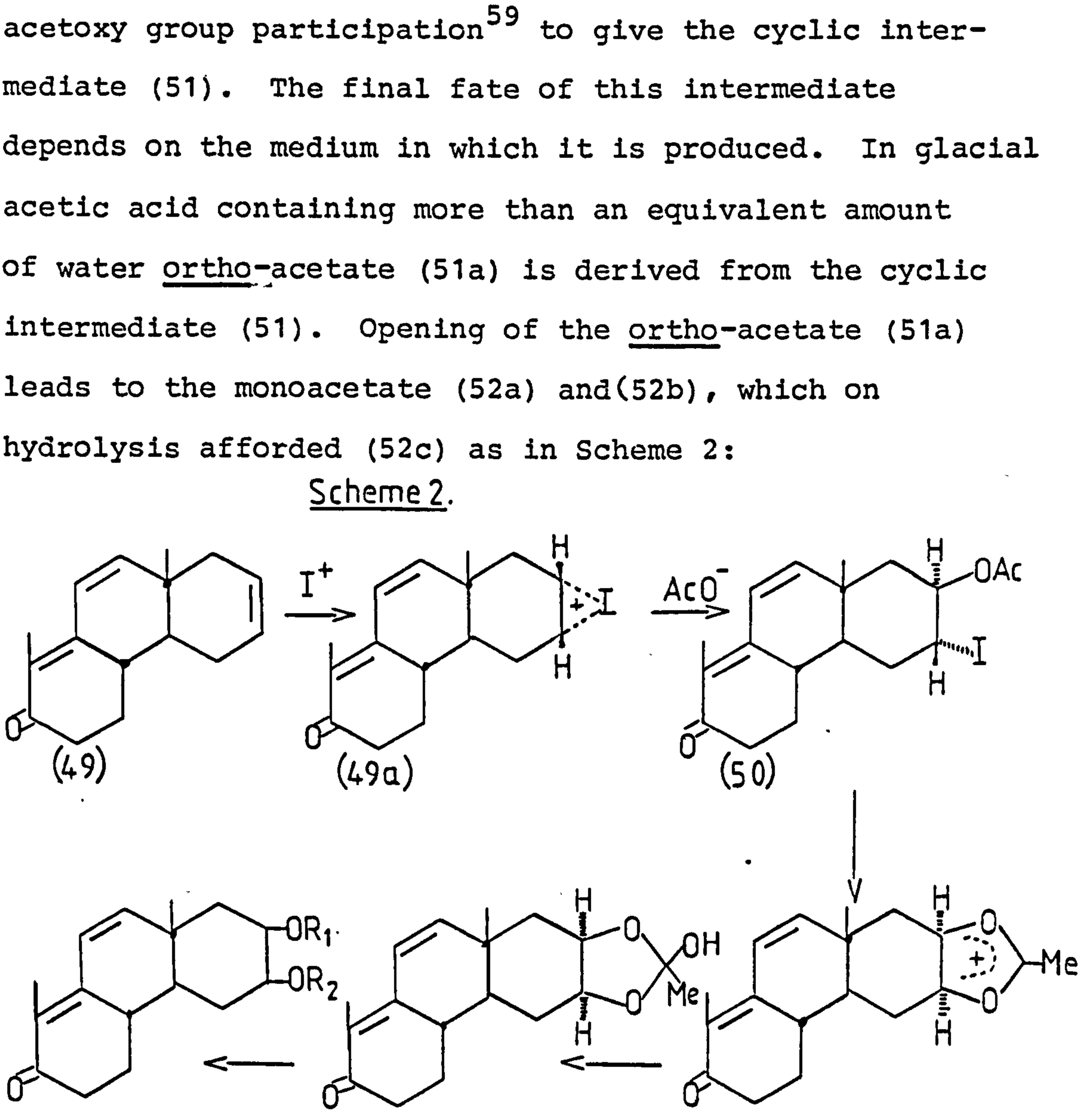


(48)

Woodward[45] reported silver acetate had a big influence in stereoid chemistry during the formation of a β-cis-glycol (52c) in the oxidation of the 6,7 double bond of (±)-anti-trans-4,4a,4b,5,8,8a-hexahydro-1,8a-dimethyl-2 (3H)-

phenanthrone (49) with iodine in wet acetic acid. Although the same author[57] had earlier reported the same compound (49) afforded an α-cis glycol as major product when osmium tetroxide was used as an oxidising reagent. The formation of the β-cis glycol was explained by the α-attack of I^+ from IOAc[58] to give an α-iodonium ion (49a), which then opened trans through β-attack of acetate to give the trans-iodoacetate (50). The subsequent replacement reaction of (50) with silver acetate and wet acetic acid involved acetoxy group participation[59] to give the cyclic intermediate (51). The final fate of this intermediate depends on the medium in which it is produced. In glacial acetic acid containing more than an equivalent amount of water ortho-acetate (51a) is derived from the cyclic intermediate (51). Opening of the ortho-acetate (51a) leads to the monoacetate (52a) and(52b), which on hydrolysis afforded (52c) as in Scheme 2:

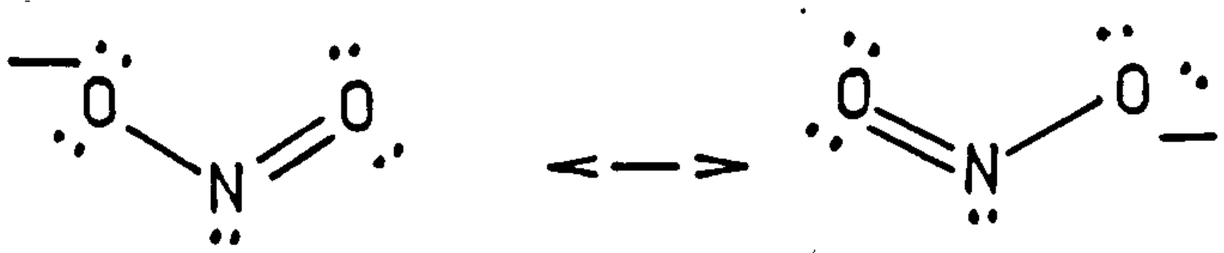
Scheme 2.



1.2.3.0. <u>General mechanism</u>.

1.2.3.1. The reaction of silver nitrite with alkyl halides has been claimed to possess characteristics of both S_N1 and S_N2 processes[77] that vary gradually with the structure of the halides. The S_N2 character is clearly seen when optically active 2-iodooctane and 2-bromooctane were allowed to react with silver nitrite either in ether, acetonitrile or benzene as solvent. The products 2-nitrooctane and 2-octyl nitrite were produced with inversion of configuration which resulted from backside nucleophilic attack on the carbon-halogen bond. The clear evidence of this attack could be seen from the inertness of neopentyl iodide with silver nitrite under the same conditions which result in complete reaction with other primary iodides such as <u>n</u>-octyl iodide.

The kinetic evidence of the reaction rate increasing on going from primary to secondary and tertiary halides showed the involvement of S_N1 processes through contribution from transition states having some carbonium ion character. The greater the S_N1 character of the transition state the greater is the preference for covalency formation with the atom of higher electronegativity.



Thus the greater yield of nitrite ester resulted when the transition state has a greater carbonium ion character and the nitrite ion undergoes covalency formation at the oxygen

atom having the higher electron density.

1.2.3.2. Hammond[62] and Hoffmann[50] then suggested that the characteristics of S_N1 and S_N2 in the reaction of alkyl halides with silver salts are best rationalised by a mechanism in which both silver cations and the accompanying anions participate in the rate determining step. The first formed product is an ion-pair intermediate composed of an anion and a carbonium ion;

$$X^- + R-Y + Ag^+ \xrightarrow{\text{slow}} X^{-}\!\!\cdots\!\!R^+ + Ag^+Y^- \quad \text{—(i)}$$

$$X^{-}\!\!\cdots\!\!R^+ \begin{cases} \xrightarrow{\text{Fast}} RX \\ \xrightarrow{\text{Fast}} \text{olefin} + HX \end{cases} \quad \text{—(ii)}$$

$Y = (I, Br, Cl)$.

The participation of the anion which is an S_N2 characteristic could be clearly seen during reactions involving equimolar concentrations of t-butyl bromide and silver tosylate, compared with the same concentrations of t-butyl bromide and silver tetrafluoroborate for which Hoffmann found the first half-life for the formation of silver bromide at 25° was about 10 times shorter for the reaction with silver tosylate.

The ion-pair intermediate is claimed as having more carbonium ion character.[61,62] The silver cation is a strong electrophile and halide ion a weak nucleophile so that interaction of silver ion with the halogen of the alkyl halide increases the degree of polarization of the

carbon-halogen bond. The rate of reaction thus increases as one proceeds from primary to tertiary halides.

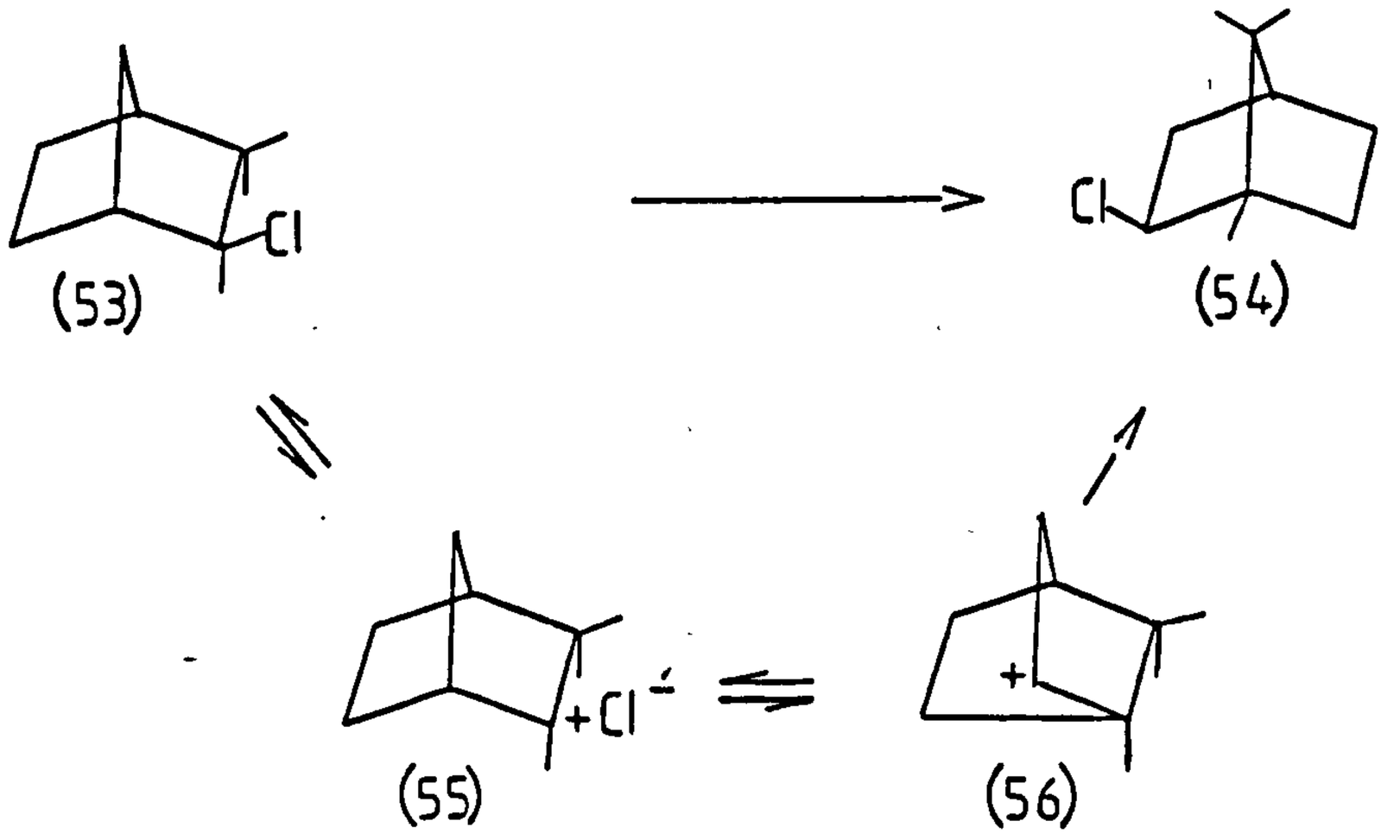
1.3.0.0. Norbornyl cation.

1.3.1.0. General introduction.

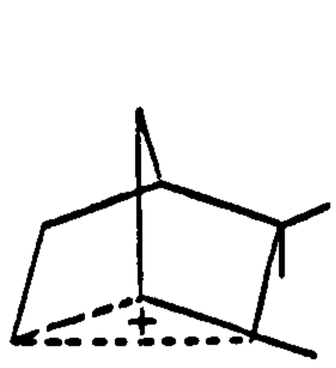
The properties of carbocations, which may be generated by reactions such as the solvolysis of alkyl halides, have been reviewed in detail by Olah[64,65,66] and Bethell.[67] The 2-norbornyl cation for which several different structures have been reported has aroused much interest.

1.3.1.1. Norbornyl cation intermediates.

Meerwein[68] was the first to suggest that the facile rearrangement of camphene hydrochloride (53) into isobornyl chloride (54) catalysed by acid, involved the equilibrating classical ions (55) and (56) in both of which the positive charge is localised on a single atom.



Subsequently Wilson,[69] suggested that the non-classical cation (57), as a transition state separating (55) and (56) during the reaction.



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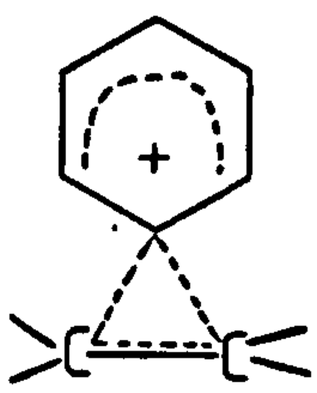

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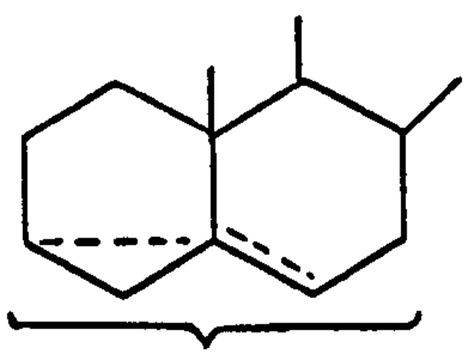


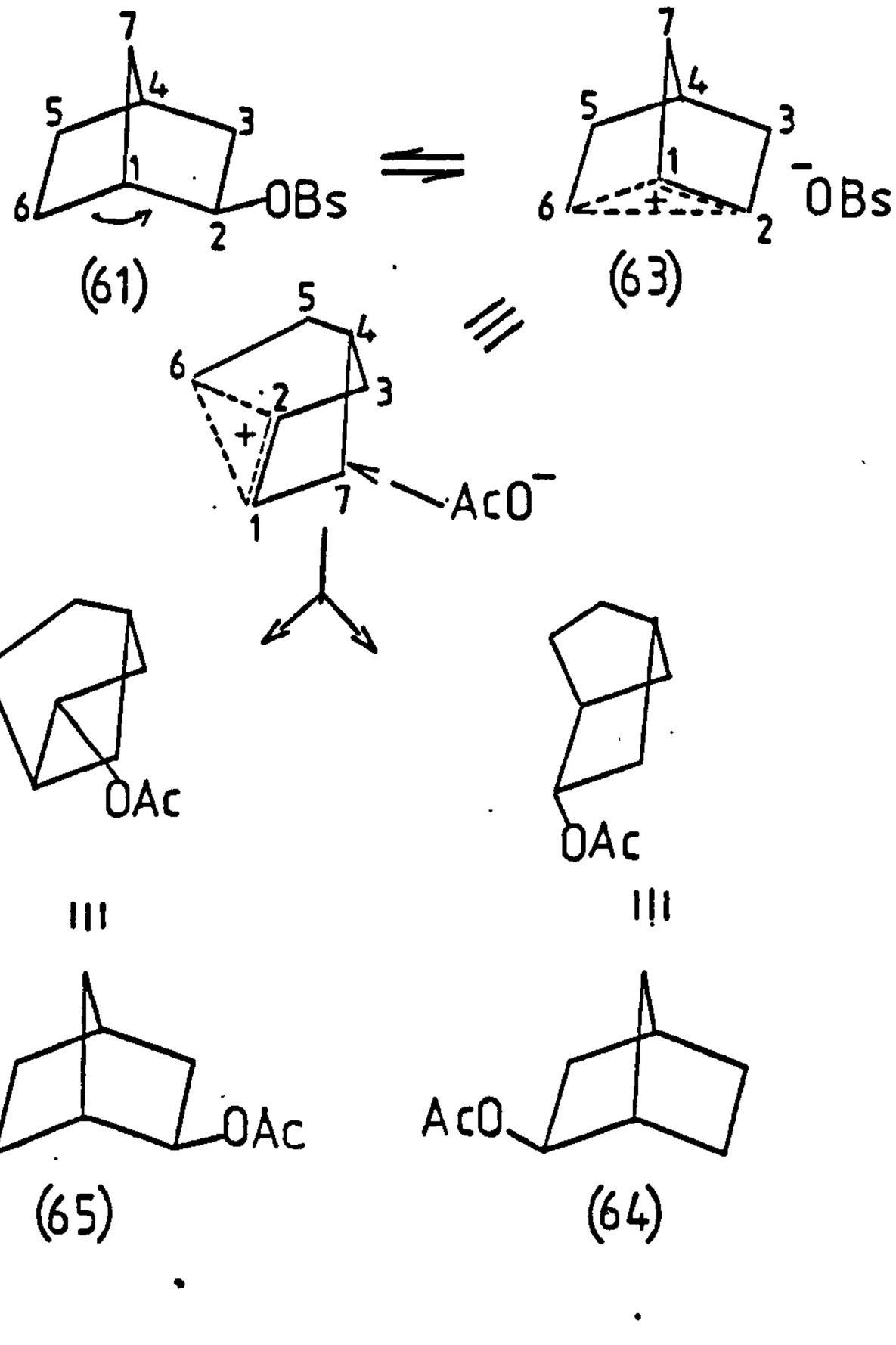
(59)

(60)

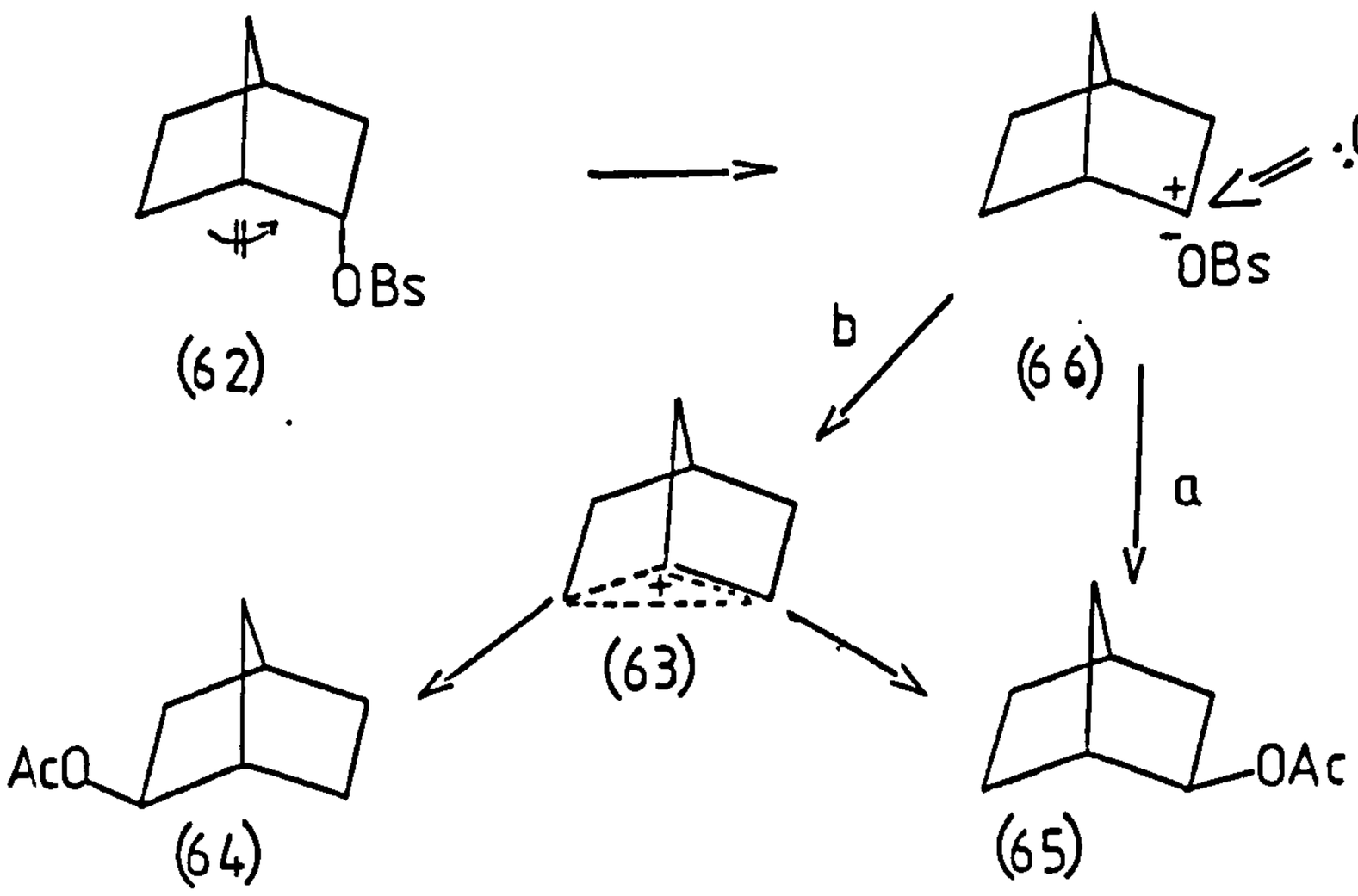
Non-classical cations were defined by Winstein[70] as employing, at least in part, overlap of orbitals on carbon atoms between which there does not occur an additional σ- bond. Such overlap is usually not π but intermediate between σ and π, such as phenonium ion (58), i-cholesteryl (59) and cyclopropyl carbinyl (60) for further examples.

Winstein et al.[71-73] studied the acetolysis of norborn-2-exo-ylbrosylate (61) and its 2-endo isomer (62), and found that the rate of solvolysis of the 2-exo-brosylate (61) relative to the 2-endo-brosylate (62) was 350 in acetic acid at 25°.

Acetolysis of the optically active 2-exo-brosylate (61) afforded racemic product 2-exo-acetates (64 and 65). Winstein proposed that the ionization of the exo-brosylate (61) was assisted by the C-1 - C-6 bonding electrons leading to the formation of the bridged non-classical ion (63) as intermediate.

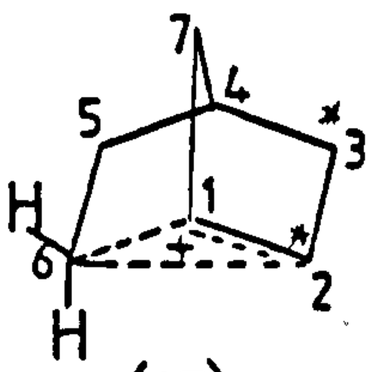


The intermediate (63) serves well to explain the formation of racemic product because the molecule has a plane of symmetry passing through C-4, C-5, C-6, and the midpoint between C-1 and C-2. The attack of acetate ion has an equal possibility at C-1 and C-2 and results in equal amounts of the racemic acetates (64) and (65).



The participation of the C-1 - C-6 bond during acetolysis of 2-endo-brosylate (62) is geometrically prohibited, and the slow rate of reaction of (62) was believed to be because of the unassisted ionization to a classical cation (66) which then co-ordinated with solvent on the side opposite to the departing group. This was followed by the partitioning between (a) collapse with solvent to give the optically active (65) and (b) re-arrangement to the symmetrical bridged ion (63) to afford a racemic acetate (64) and (65).

The intermediate symmetrical bridged ion (67) was subjected to experimental studies by Roberts, Lee and Saunders[74,75] during acetolysis of the 2-exo-brosylate (61) labelled with ^{14}C at the C-2 and C-3 positions. They thought that if racemization of the optically active brosylate results either from (67) or from rapid equlibration of classical 2-norbornyl cations (69), 25% of the total initial ^{14}C should be found at each of the C-1, C-2, C-3 and C-7 positions in the acetate produced.



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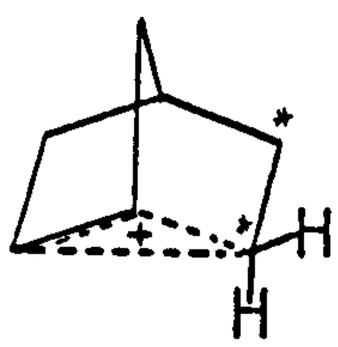
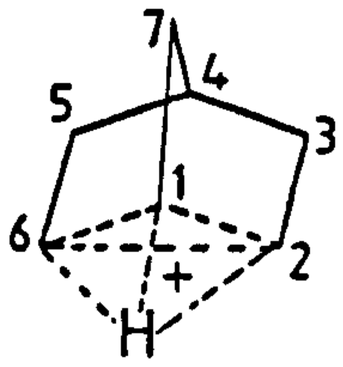
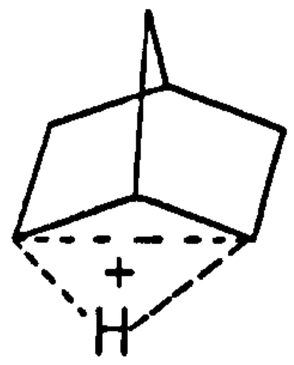


(68)

(69)

(70)





(71)

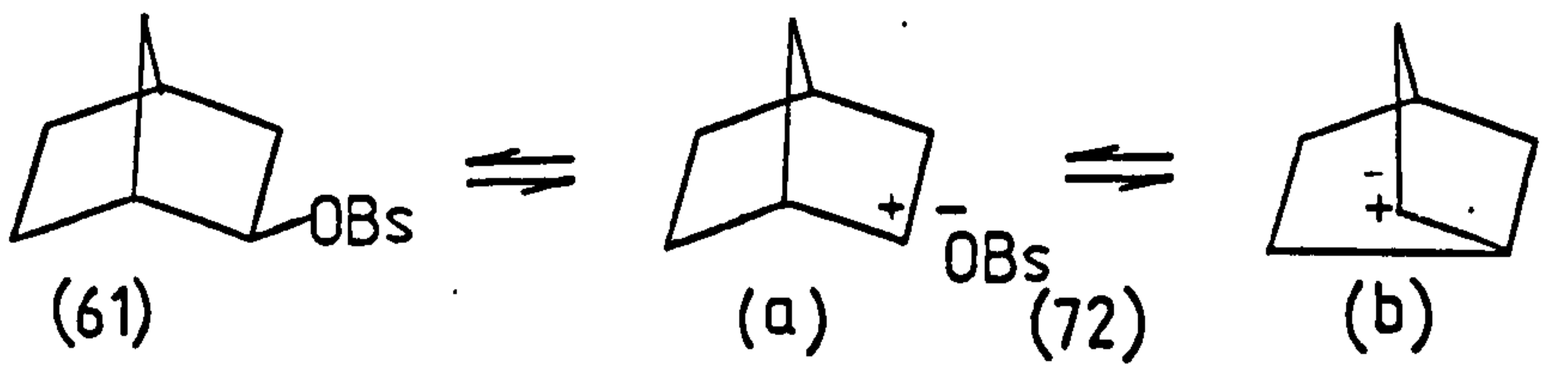
They observed from the experimental data, the ^{14}C distribution at C-2 + C-3 (40%), C-1 + C-4 (23%), C-7 (22%) and C-5 + C-6 (15%). They suggested the ^{14}C distribution

was best suited to the notricyclonium ion (70), in which carbon atoms 1, 2 and 6 are totally equivalent compared to the bridged ion (67). Nucleophilic attack by solvent at any of C-1, C-2, and C-6 in (70) leads to racemic 2-exo-acetates (64) and (65).

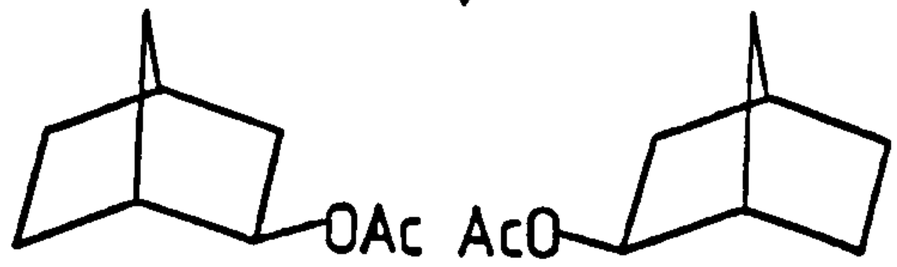
The notricyclonium ion (70) which Roberts et al. regarded as an intermediate was disputed by Winstein,[72] and Roberts,[74] agreed that ^{14}C scrambling could also be interpreted as arising from the inter-conversion of one bridged ion (67) into another (68) by means of 6,2 and 6,1 hydride shifts. (Position 1 and 2 on the norbornyl nucleus are totally equivalent in the bridged ion (67)). The two bridged ions (67) and (68) are identical except for the position of radioactive carbon.

Winstein and Trifan[72,76] further suggested that an "edge-protonated" cyclopropane intermediate (71) might well be involved, rather than the "face-protonated" cyclopropane species, the notricyclonium ion (70).

In contrast to the views of Winstein and Roberts, Brown[77a,b,c] believed the rate of acetolysis of the 2-exo-brosylate (61) is normal. Ionisation of (61) to give classical ion (72a) is unassisted by the C-1 to C-6 bonding electrons. A rapid equilibrium of (72a) with the other classical ion (72b) is set up and capture of these classical ions by acetate ion afford the racemic acetates (64) and (65).



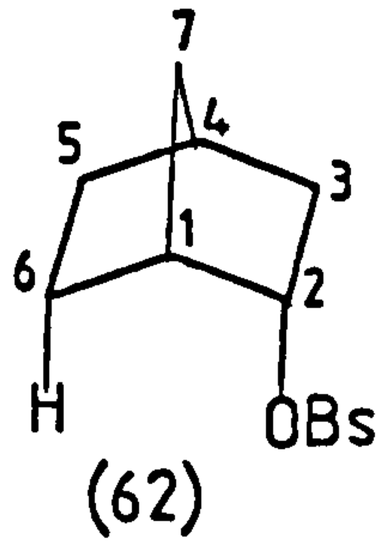
(61) (a) (72) (b)



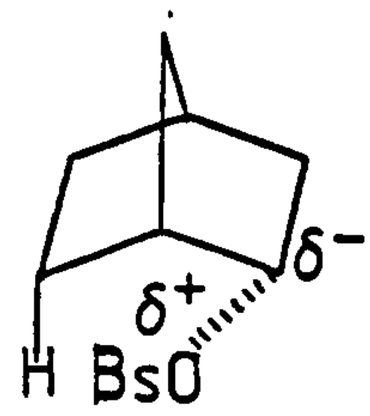
(65) (64)

Brown accounted for high exo-endo ratios observed in the rate of acetolysis on the basis of an unusually slow endo rate.

7



(62)

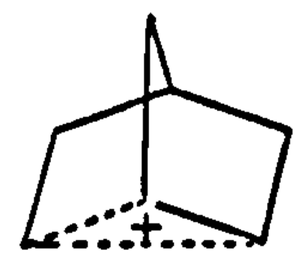


(73)

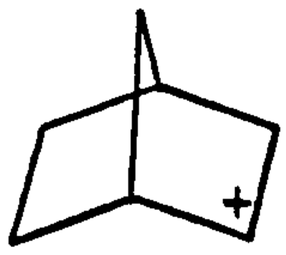
An examination of the preferred path for the leaving group in the endo derivatives such as (62) reveals that this path brings the departing brosylate group very close to the opposite side of the rigid endo proton at C-6, which increased the steric strain in the transition state (73), before equilibrating to ion pairs (72). Brown also pointed out that if a σ-bridged ion such as (63) was not involved, the barrier for interconversion of (72a) and (72b) must be very low. If the rate of interconversion of (72) is to be fast relative to the rate of their capture by solvent, the barrier must indeed be low, not

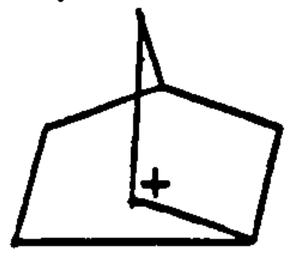
greater than a few kcal mol^{-1}.

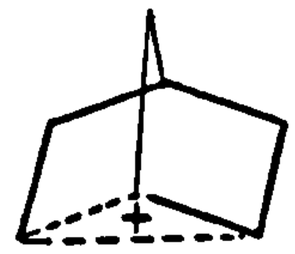
Fig. 1



transition state

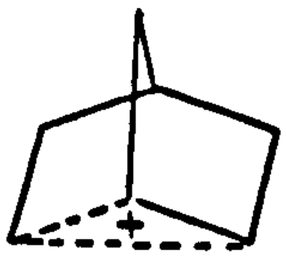




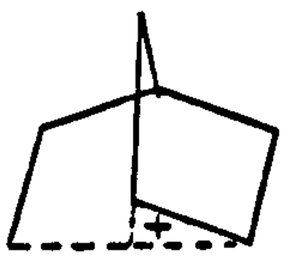


intermediate

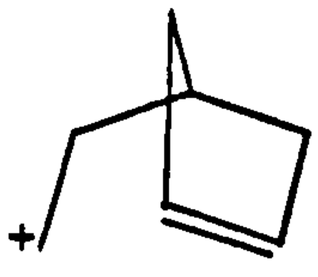
In essence, the non-classical proposal was that those electronic effects which served to lower the barrier for interconversion of two cations (Fig. 1) could further stabilize the transition state species into a symmetrical intermediate sufficiently stable that there was no longer any need to consider the original equilibrating unsymmetrical cations.



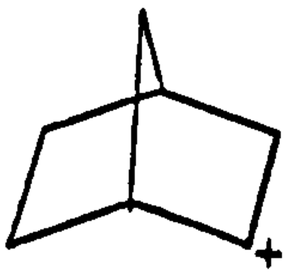
(74)



(75)



(76)



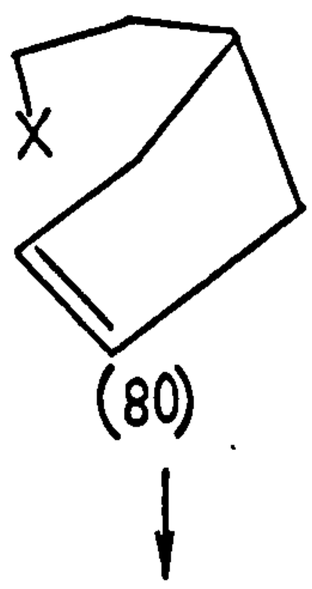
(77)

Subsequently Olah, first favoured a formulation of the norbornyl cation as a corner protonated notricyclene (74),[78] deleting the dashed double bond of Winstein in (63), and he followed later with a second formulation as (75),[79]

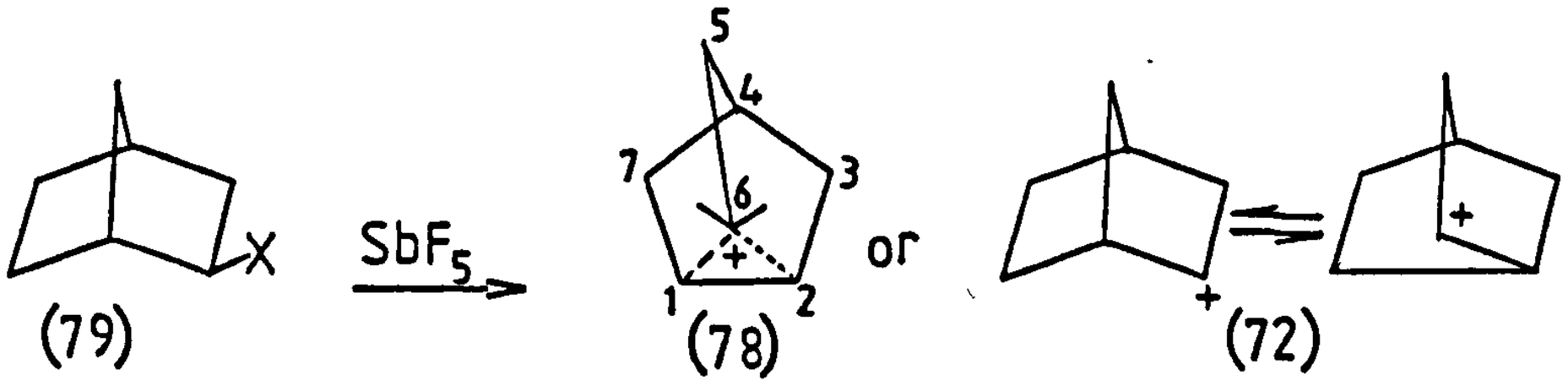
Dewar preferred the formulation as π complex (76)[80] and finally Taylor supported a formulation of the 2-norbornyl cation as involving vertical stabilization by the C-1 - C-6 bonding pair, without σ-bridging or movement of the atoms in (77).[81]

1.3.1.2. NMR studies of norbornyl cation structures at low temperature

The classical non-classical controversy[82] concerning the structure of the norbornyl cation (78) encouraged Olah and his workers to generate and observe the norbornyl cation spectroscopically in solutions of low nucleophilicity.[83] He found that preparation of the ion by the "σ-route" from 2-norbornyl halides (79), by the "π-route" from β-Δ^3-cyclopentenyl ethyl halides (80), and by the protonation of notricyclene (81) all led to the same norbornyl cation (78).



(80)



(79)

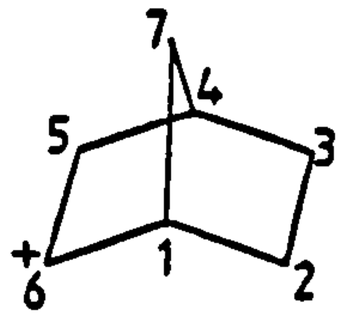
(82); X = F

(78)

(81)

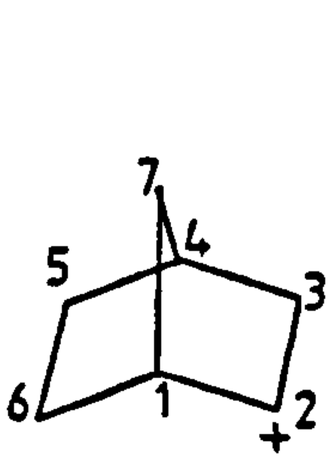
(72)

Saunders, Schleyer and Olah[84] first observed the ^1H nmr spectrum of the norbornyl cation prepared from 2-exo-fluoronorbornane (82) in SbF_5 - SO_2. At room temperature the ^1H nmr spectrum consisted of a single broad peak at $\delta 3.75$ due to scrambling of all hydrogen atoms, which contrasted with the spectrum of the starting (82) having a multiplet at $\delta 4.95$, a broad doublet at $\delta 4.0$, a multiplet at $\delta 2.3$ and a multiplet at $\delta 2.0$ - $\delta 0.8$. The equilibration of the hydrogen atoms is caused by fast 3,2- and 6,2- hydride shifts and Wagner-Meerwein rearrangement.

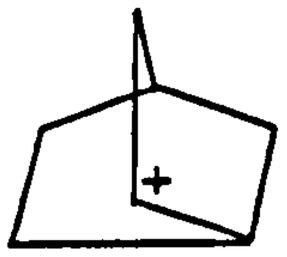


6,2-Hydride shift

fast

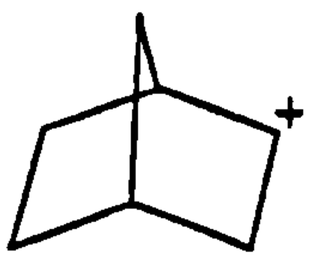


fast



Wagner-Meerwein rearrangement

fast



3,2-Hydride shift

When the temperature was lowered to -70°, the spectrum of the 2-norbornyl cation resolved into three peaks with relative area 4:1:6 and did not change when the temperature was further lowered to -120°.[85] The spectrum was interpreted as evidence that 3,2-hydrogen shift was frozen out, but the 6,2- hydrogen shift and Wagner-Meerwein rearrangement are still fast. Then Olah et al.[85] succeeded in "freezing out" on the nmr time scale, the fast 6,2- hydrogen shift. Using a mixed SbF_5 - SO_2ClF - SO_2F_2 solvent system they observed the spectrum down to -156°. At -128° to -150° significant changes occurred, the low-field peak due to the four equilibrating "protonated cyclopropane" ring protons [m δ5.0 at -70° to -120°] broadened and then separated into two resonances, each of relative area two, at δ3.05 (H-6) and δ6.59 (H-1, H-2). The high-field resonance due to the six methylene protons broadened, developing a shoulder at δ1.70 (2H-3,

2H-5, and 2H-7), while the peak at 2.82 of H-4 remained unchanged.

With the help of the ^{13}C spectra, Olah[85] concluded that the ion is non-classical, with all rearrangements "frozen-out". The structure of the ion is that of the methylene bridged pentacoordinated ion (78) obtained at lower temperature (-150^{o}). The spectrum is shown to have resonance at δ125.3 (C-1 and C-2), δ22.4 (C-6), δ33.4 (C-4), δ48 (C-3 and C-7), and δ28 (C-5). In comparison the spectrum at -70^{o}, when there is rapid equilibration within the norbornyl cation, consists of three carbon resonances at δ92, 37.7 and 31.3 for equilibrating C-1, C-2, C-6, bridge head C-4, and equivalent methylene carbons (C-3, C-5, and C-7), respectively. The pentacoordinated bridging methylene carbon atom is not deshielded (δ22.4), whereas the tetracoordinated carbons to which bridging takes place (which carry more positive charge) is deshielded (δ125.3).

In the proton-coupled ^{13}C spectrum, no coupling was observed between the methylene hydrogens at the pentacoordinated carbon (C-6) and the cyclopropane-like carbons (C-1 and C-2), which is expected from the non-classical structure since the two-electron, three centre bonds are longer and weaker than normal Csp3 - Csp2 bonds.

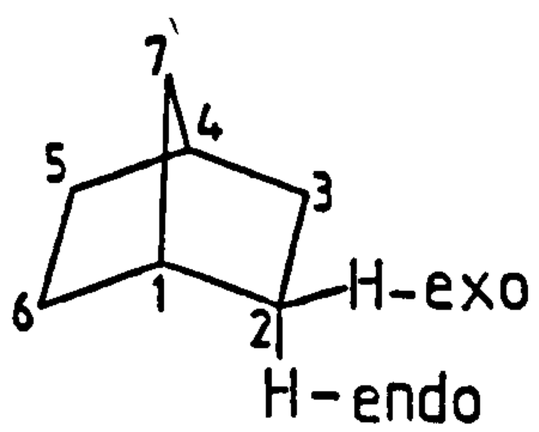
1.4.0.0. NMR of norbornyl, norbornenyl, and norbornadienyl derivatives.

1.4.1.1. General Introduction.

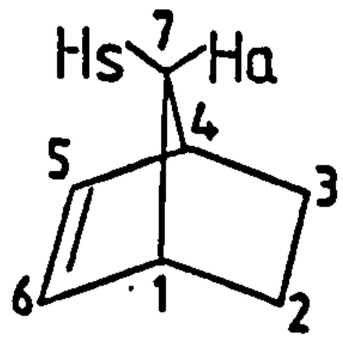
The cage-like structure[63] of norbornanes, norbornenes, and norbornadienes which brings more groups within distances at which long-range shielding effects are expected to be significant results in

(i) a large difference in the magnetic shielding between exo and endo protons, showing longer deshielding for the exo-protons; (ii) the coupling constants between each pair of adjacent protons, J(H exo - H exo) and J(H endo - H-endo), being not equal; and (iii) fairly large long-range spin-coupling constants.

1.4.1.2. Chemical Shift.



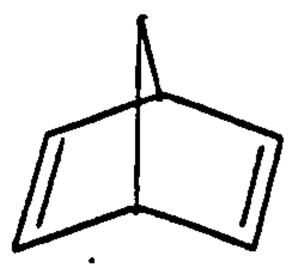
norbornane



norborn-5-ene

Ha = anti

Hs = syn



norbornadiene

The differences in chemical shift of protons in the norbornane, norbornene and norbornadienes is summarised in Table 1.

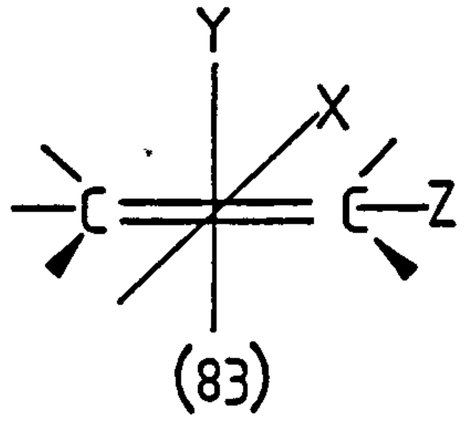
TABLE 1 (δ in p.p.m.)

Norbornane δ	Norbornene δ	Norbornadiene δ	Proton	Reference
2.20	2.83	3.53	1	
1.49	1.57	6.66	2-exo	
1.18	0.94	-	2-endo	63,87
1.49	1.57	6.66	3-exo	
1.18	0.94	-	3-endo	
2.20	2.83	3.53	4	
1.49	5.95	6.66	5-exo	
1.18	-	-	5-endo	
1.49	5.95	6.66	6-exo	
1.18	-	-	6-endo	
1.49	1.07	1.95	7-anti	
1.21	1.32	1.95	7-syn	

The chemical shift of the protons in the norbornyl, norbornenyl and norbornadienyl derivatives as for other organic compounds is dependent[63] on the neighbouring substituents and on the anisotropy of carbon-carbon double bonds, the carbonyl group and oxygen atoms.

The proton is deshielded and would resonate at lower field if the electron density round the atom is reduced as a result of electron withdrawal by the neighbouring atoms.

The deshielding of the olefinic protons is attributed mainly to the anisotropy of the π-system, rather than the inductive effect. Experimental measurements of the double bond anisotropy indicate that protons lying near the X- and Z- axis (83) will be deshielded, while those in the vicinity of the Y-axis will be shielded. Both of the effects could be seen in Table 1 and Table 2.



(83)

TABLE 2

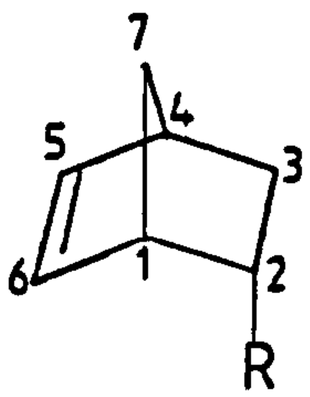
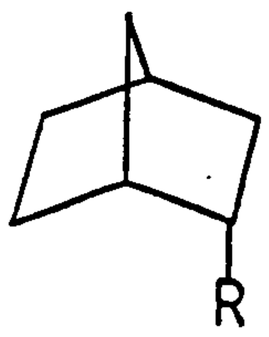
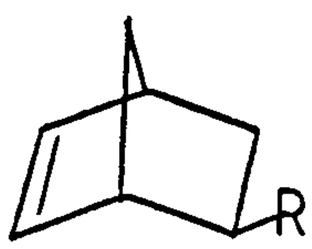
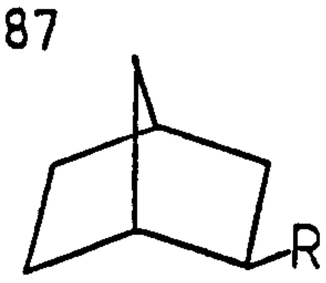
	R	H-1	H-2	H-3exo	H-4	References
84 	OAc	3.12	5.17	2.10	2.84	86,88,89
	NO_2	3.53	4.94	2.14	3.0	
	Cl	3.10	4.47	2.27	2.90	
	Br	3.10	4.24	2.27	2.82	
	Ph	2.95	3.32	2.14	2.90	
	CO_2Me	3.12	2.87	-	2.82	
	CO_2Et	3.16	2.86	1.84	2.86	

TABLE 3

Compound	R	H-1	H-2	H-3exo	H-4	References
85 	OAc	2.40	4.87	2.0	2.20	89
86 	OAc	3.20	4.57	2.30	2.85	
87 	OAc	2.48	4.54	2.0	2.20	

It is observed that in the compounds (84; R = OAc), (85), (86) and (87), the 2-endo proton resonates at higher field than the corresponding 2-exo proton. The effect is believed not to be due to the anisotropy of the double bond, but it is thought might be as an analogy[90] to the well known generalisation about the relative chemical shifts of axial and equatorial protons in six membered rings, for which equatorial protons are shifted downfield[63] compared to axial protons.

1.4.1.3. Vicinal and geminal coupling constant .

Generally for norbornanes and norbornenes, we would find;

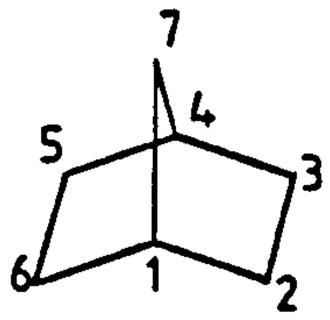
a) Geminal coupling > vicinal coupling

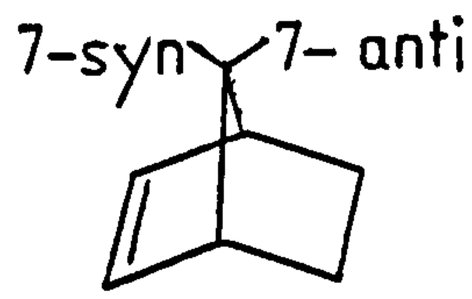
b) cis coupling > trans coupling

c) The bridge head, H-1 proton couples with H-2-exo but not with H-2-endo .

d) The couplings of a bridge head H-1 proton with the bridge H-7syn and H-7anti protons are non-equivalent in norbornenes and J1,7-syn is about (1.8-2.0)Hz and J1,7-anti is about (1.0-1.4)Hz .

Value of coupling constants in norbornane and norbornene.





J(2-exo, 2-endo)12-20

J(2-endo, 3-endo)6-7

J(2-exo, 3-exo)9-10

J(1,2-exo)3-4

J(1,2-endo) 0

J(2-endo, 3-exo)2.5-5.0

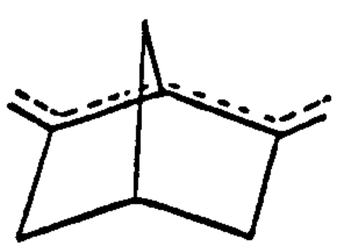
J(5,6)5-6

J(1,6)2.2-3.3

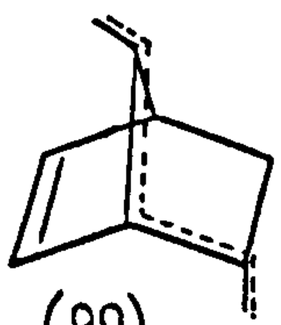
J(1,7-syn or anti)0-3.3

1.4.1.4. Long-range coupling constants.

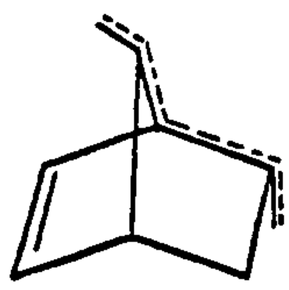
Long range coupling[63,92] across four single bonds are also useful in stereochemical determinations for norbornanes, norbornenes and norbornadienes. In common with other systems it has been found that effective couplings across four bonds only occur when they are in a planar, W-configuration. The amount of coupling constants in the norbornyl and norbornenyl systems are generally in the range of (1-3Hz). The long range couplings which are useful in the structure determinations are between H-3-exo and H-5-exo (88), H-2-endo and H-7-syn (89) and between H-3-endo and H-7-syn (90).



(88)

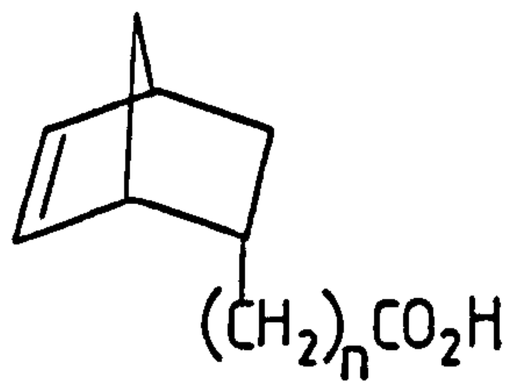


(89)



(90)

1.5.0.0. Aims and objectives of research.



Davies and Dowle[93,94] studied the iodolactonisation of the norbornene carboxylic acid derivatives (n = 1,2) and the acid catalysed cyclisation of the carboxylic acid derivatives (n = 0,1). As a sequel to this investigation it was proposed to study the lactonisation of acids having a longer carboxylic acid side chain, and also to investigate the reaction of norbornane iodolactones with silver tosylate. It was hoped that these reactions would lead to the isolation of compounds of novel structure and also provide further information on reactions and rearrangements of norbornyl cations.

2.0.0.0. CHAPTER 2: DISCUSSION.

2.1.0.0. Synthesis of norbornenylcarboxylic acid derivatives.

2.1.1.0. Scheme 1

(96) R=Me.
(97) R=Ph.

(i) H_2O ; (ii) MeOH ; (iii) NaOH ; (iv) H^+.

2.1.1.1. The Diels-Alder addition of cyclopentadiene to acrylic acid,[95] maleic anhydride,[96] fumaryl chloride,[95] crotonic acid,[100] crotonyl chloride,[95] cinnamic acid[97] and cinnamoyl chloride[102] gave norborn-5-en-2-ylcarboxylic acid (91), norborn-5-en-2-endo, 3-endo-yldicarboxylic acid anhydride (92), norborn-5-en-2-endo, 3-exo-yldicarboxylic acid (95), 3-methylnorborn-5-en-2-ylcarboxylic acid (96) and 3-phenylnorborn-5-en-2-ylcarboxylic acid (97) respectively as is reported in the literature.

The reaction conditions and the product yields are dependent on the dienophile. The acid chlorides from fumaric acid, trans-crotonic acid, and trans-cinnamic acid are found to be more reactive and gave better yield than the corresponding acids. Although the dienophiles have the same conjugation system, the reactivity of the acid chlorides are enhanced by the chlorine atom which is a stronger electron withdrawing group than is the hydroxyl group in the acid.

Maleic anhydride is a powerful dienophile and forms the anhydride (92) on reaction with cyclopentadiene at room temperature for several minutes. The anhydride (92) when subjected to hydrolysis in water gives norborn-5-en-2-endo,3-endo-yldicarboxylic acid (93) in 84.6% yield (Lit.[96] 92%). Reaction of (92) with anhydrous methanol[98] affords the half ester (94) in 87% yield (Lit.[98] 82%).

TABLE 1. Yields of Diels-Alder adducts with Cyclopentadiene.

Diene	Dienophile	Reaction Conditions	Product	%Yield	Literature Yield
Cyclopentadiene	acrylic acid	Heated at 60° for 3 h	91	63	50[95]
	maleic anhydride	room temperature 30 min	92	56	78.8[96]
	trans-fumaryl chloride	-10° for 1 h and room temperature (16 h)	95*	73	82[95]
	trans-crotonic acid	Heated at reflux for 4 h	96	21	30[100]
	trans-crotonyl chloride	-10° for 1 h and room temperature (16 h)	96*	54	-[95]
	trans-cinnamoyl chloride	room temperature for 96 h	97*	51	-[102]

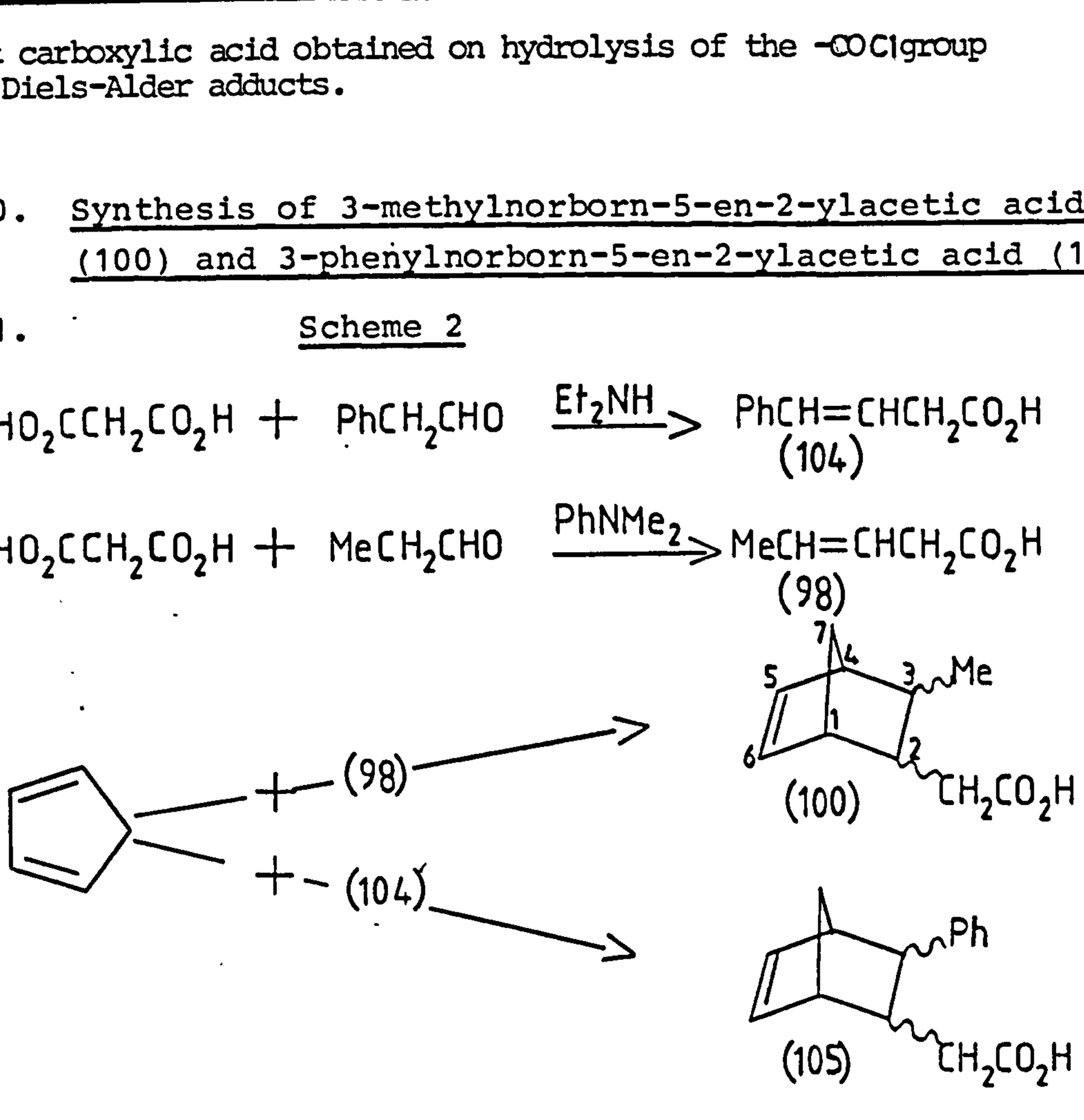
*Product carboxylic acid obtained on hydrolysis of the -COCl group in the Diels-Alder adducts.

2.1.2.0. Synthesis of 3-methylnorborn-5-en-2-ylacetic acid (100) and 3-phenylnorborn-5-en-2-ylacetic acid (105).

2.1.2.1. Scheme 2

$$HO_2CCH_2CO_2H + PhCH_2CHO \xrightarrow{Et_2NH} PhCH{=}CHCH_2CO_2H \quad (104)$$

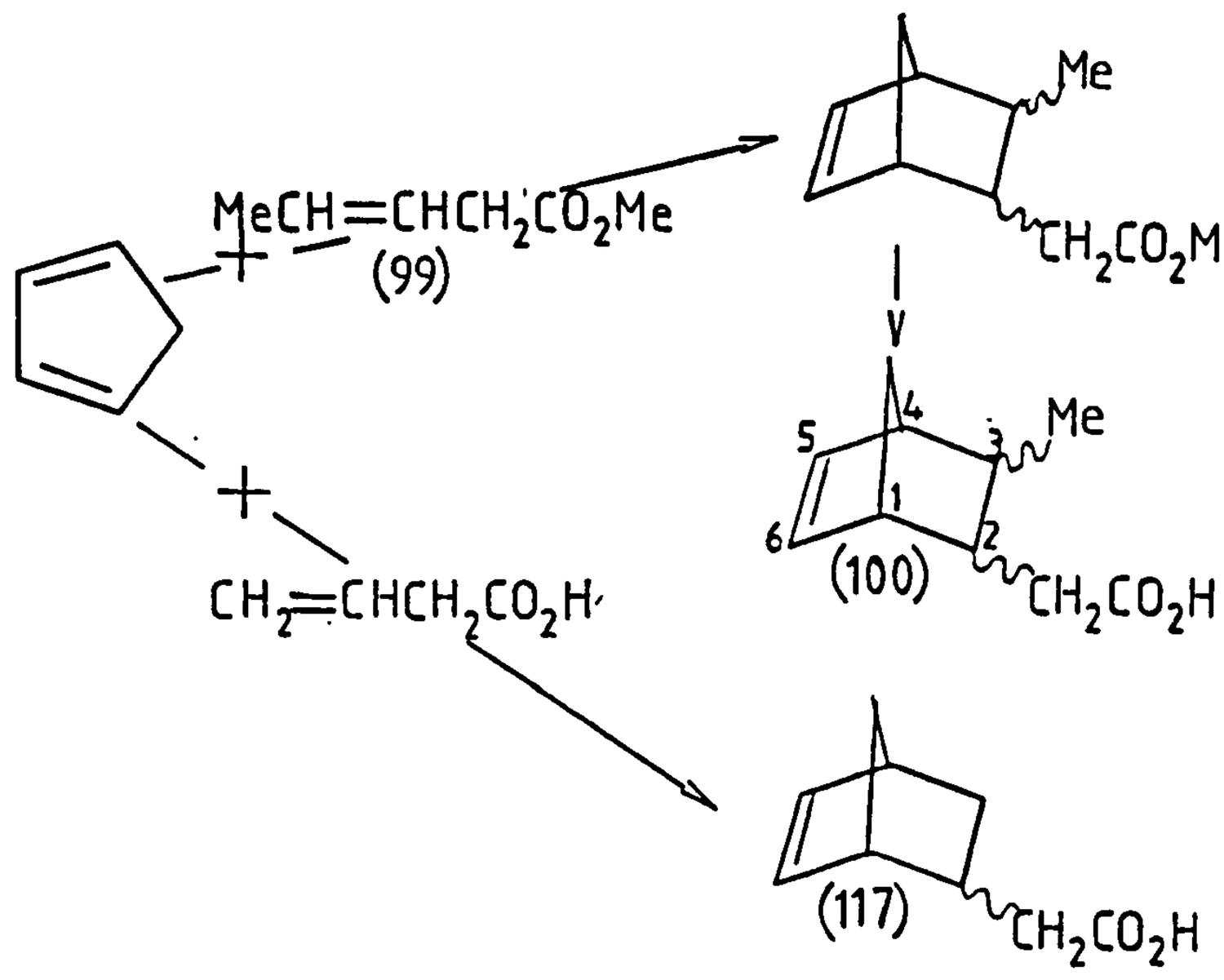
$$HO_2CCH_2CO_2H + MeCH_2CHO \xrightarrow{PhNMe_2} MeCH{=}CHCH_2CO_2H \quad (98)$$



Preparation of the acids (100) and (105) requires pent-3-enoic acid (98) and 4-phenylbut-3-enoic acid (104) as the dienophiles, which should give (100) and (105) on addition to cyclopentadiene in the Diels-Alder Reaction.

Pent-3-enoic acid (98) was prepared by the condensation[103] of propionaldehyde with malonic acid in the presence of dimethylaniline. The mixture was stirred at room temperature for 48 h and subjected to decarboxylation by heating on the steam bath for 18 h, followed by acidification, extraction, and distillation to afford pent-3-enoic acid (98) in 20% yield; b.p. 120° at 30 mm Hg. (Lit.[103] yield 23%, b.p. 90° at 10 mm Hg). 4-Phenylbut-3-enoic acid[105](104) was obtained by refluxing a solution of phenylacetaldehyde and malonic acid with diethylamine in absolute alcohol for 6 h. The product was obtained in 42% yield, m.p. 85-87° (Lit.[105] yield 60%, m.p. 87°).

2.1.2.2. Scheme 2A



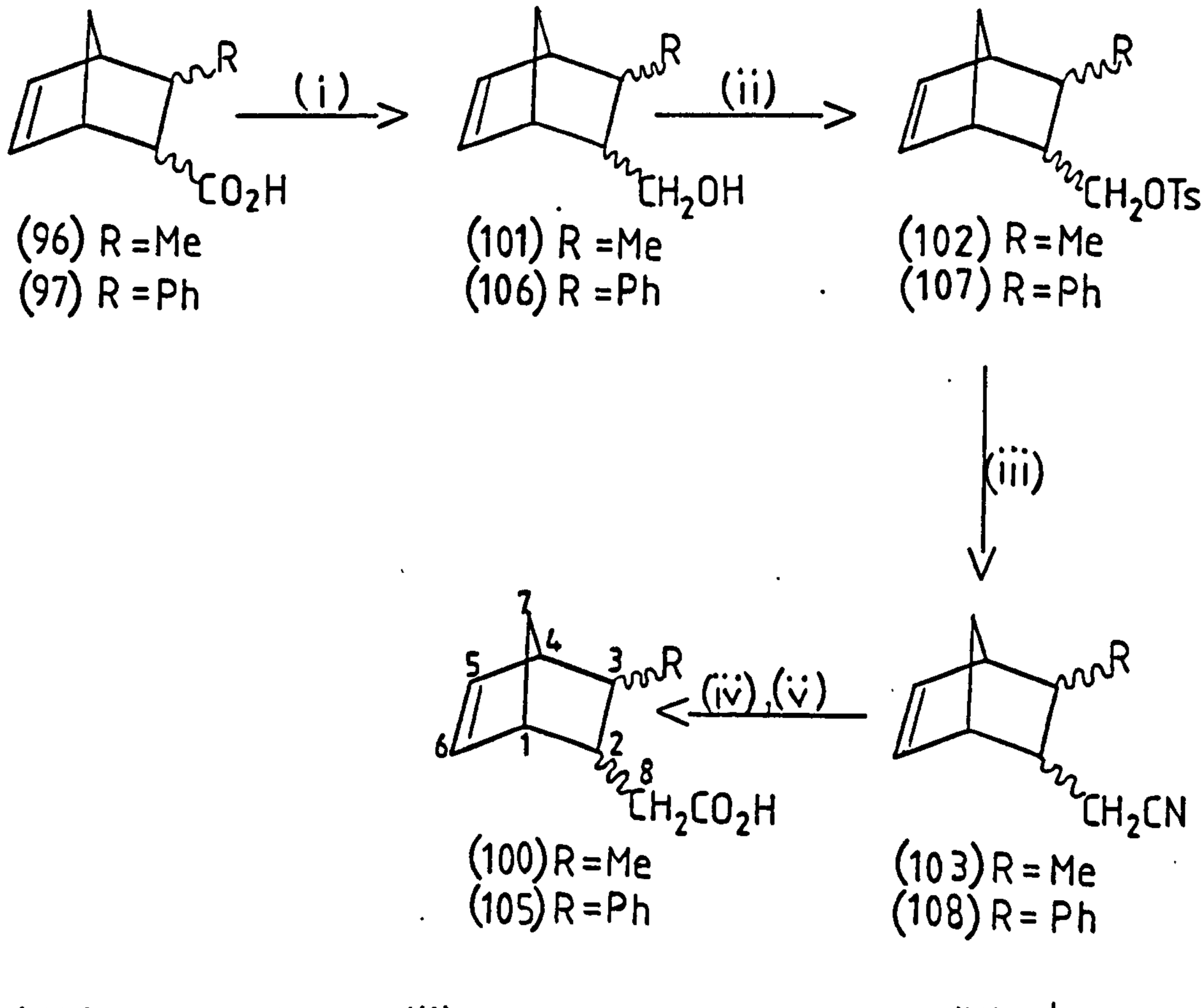
Alder and Windemuth[109] obtained norborn-5-en-2-ylacetic acid (117) by heating a mixture of cyclopentadiene and vinylacetic acid in a sealed tube for 8 h. Based on their method, a mixture of cyclopentadiene and pent-3-enoic acid (98) was heated in a sealed tube at 180° for 18 h, unfortunately the reaction mixture when worked up showed only the presence of unreacted starting acid (98) together with polymeric material.

A second attempt was made by heating methylpent-3-enoate (99) and cyclopentadiene in a sealed tube at 180° for 72 h. The solidified product was shaken with chloroform, and the insoluble material removed by filtration. The filtrate was evaporated to give a yellow viscous oil which on hydrolysis with 5% aqueous sodium hydroxide, acidification and extraction afforded the required 3-methylnorborn-5-en-2-ylacetic acid (100), in 5.6% yield.

The yield of the acid (100) was slightly improved by using a longer reaction time; a yield of 10.6% was obtained when the mixture was heated at 180° for 200 h. The ^{1}Hnmr of the acid (100) shows a brs at δ9.63 (COO<u>H</u>), a m at δ6.10 (H-5, H-6), a brs at δ2.80 (H-1), a brs at δ2.40 (H-4) and an overlapping multiplet from δ2.20 - δ1.08.

4-Phenylbut-3-enoic acid (104) and cyclopentadiene when heated in a sealed tube at 180° for 30 h give a product mixture from which the only recognisable material to be isolated was 4-phenylbut-3-enoic acid (104).

2.1.2.3. Scheme 3



(i) $LiAlH_4$; (ii) Ts-Cl ; (iii) KCN – DMSO ; (iv) NaOH ; (v) H^+.

The extension of the carboxylic acid side chain in (96) and (97) as in Scheme 3 was chosen as the alternative route for the preparation of the acids (100) and (105). Reduction of 3-methylnorborn-5-en-2-ylcarboxylic acid (96) and 3-phenylnorborn-5-en-2-ylcarboxylic acid (97) by lithium aluminum hydride for about 2 h gave the alcohols (101) and (106) in yields of 70% and 81% respectively. The alcohols (101) and (106) had similar ir spectra which showed a medium absorption at 3400 cm^{-1} (OH). In the ^1H nmr, the olefinic protons of the norbornene ring showed a m at δ6.10 for both compounds. The $>\underline{CH_2}$-O- protons for the

alcohol (101) is a m at δ3.30 and a m at δ3.50 for the alcohol (106). Treatment of each of the alcohols (101) and (106) with tosyl chloride in pyridine, using the method of Marvell and Sekera,[110] gave the corresponding tosylates (102) and (107) in yields of 95% and 78% respectively. The reactions were carried out at 0° for 1 h and then in the refrigerator for about 60 h. The precipitation of the white crystalline needles of pyridinium hydrogen chloride in the reaction mixture is the first evidence that the product tosylates are formed. The ir spectrum showed a loss of a medium absorption at 3400 cm^{-1} of (OH in starting alcohols 101 and 106) and formation of a new weak absorption at 1620 cm^{-1} (Aromatic). The ^1H nmr spectrum of (102) and (107) showed doublets at δ7.75 and 7.35, J(ortho, meta) = 8 Hz, each integrating for two protons corresponding to the ortho and meta protons in aromatic ring. A m at δ6.0 is due to the olefinic protons, with multiplets of $>\underline{CH_2}-O-$ at δ3.70 in (102) and at δ4.0 in (107). 3-Methylnorborn-5-en-2-ylmethyl tosylate (102) and 3-phenylnorborn-5-en-2-ylmethyl tosylate (107) were readily converted to the respective nitriles (103) and (108) in 78% and 82% yield when heated with potassium cyanide in DMSO for 16 h. The product nitriles (103) and (108) exhibited a medium absorption at 2250 cm^{-1} ($-C\equiv N$) in the infrared and the ^1H nmr showed a complete loss of the two d at δ7.75 and 7.35 due to ortho and meta protons in the aromatic ring and a m at δ3.70 and 4.0 for $>\underline{CH_2}-O-$ in starting tosylates (102) and (107) respectively. Base hydrolysis with 10% aqueous potassium hydroxide of the nitriles (103) and (108) by heating at 100° for 60 h,

followed by acidification and extraction, gave the required 3-methylnorborn-5-en-2-ylacetic acid (100) and 3-phenylnorborn-5-en-2-ylacetic acid (105) both in 77% yield. The ir spectrum of both acids (100) and (105) exhibited a medium broad absorption at 3300-2500 (-COO<u>H</u>), and a strong absorption at 1710 cm^{-1} (>C=O of -COOH). The ^1H nmr of the acid (100) was mentioned earlier, while the acid (105) showed a brs at δ11.5 (-COO<u>H</u>), a m at δ7.20 (-Ph), a m at δ6.20 (olefinic protons) and higher field protons at δ2.90-1.65. The acids (100) and (105) gave a molecular ion, m/e ($M^{+\cdot}$) at 168 and 228 respectively in the mass spectra.

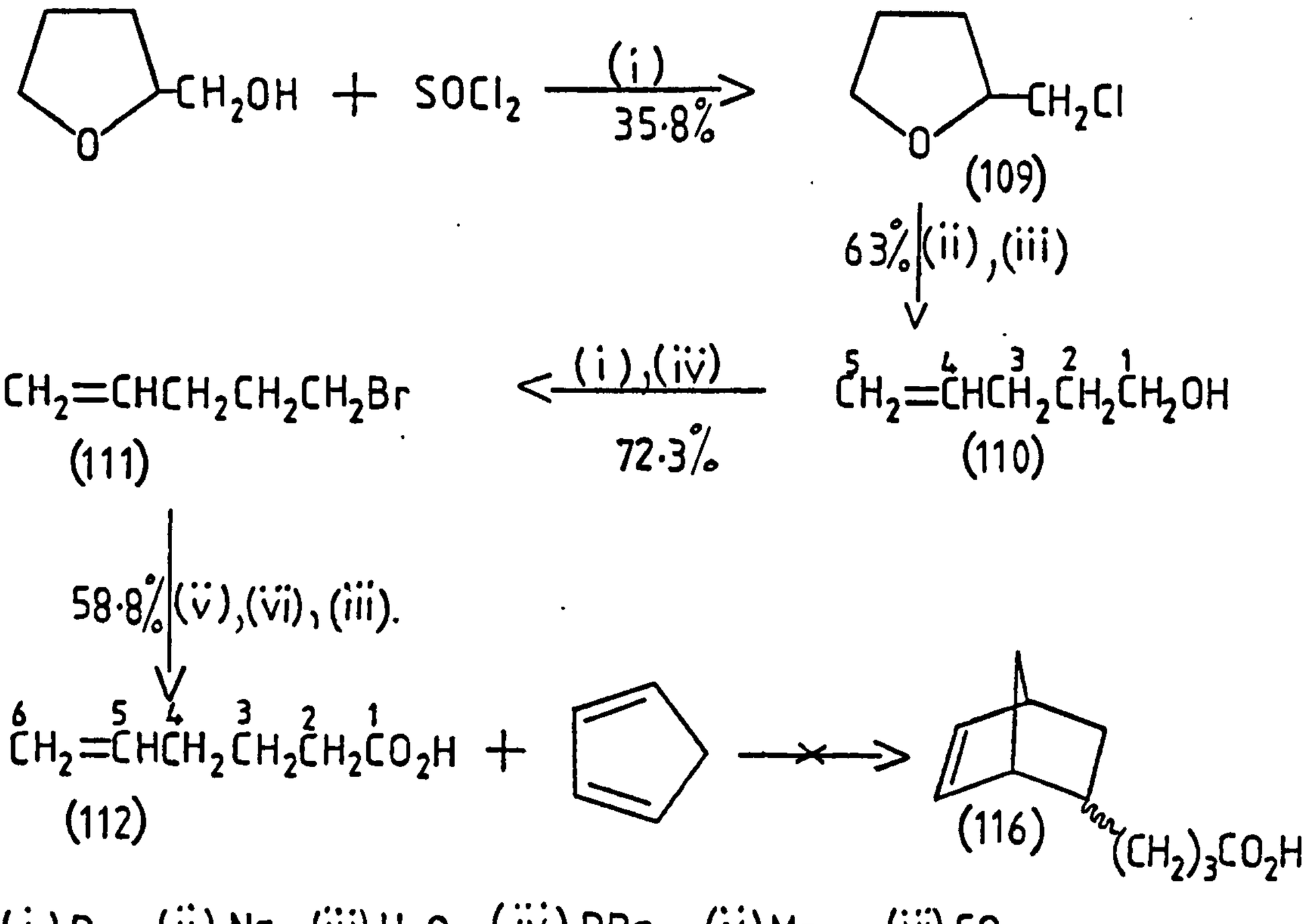
TABLE 2. Summary of the nmr data in the preparation of the acid (100) and (105).

Compounds	δ (in p.p.m.)													
	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	OH	COOH	R	ortho	meta	p-CH_3
96	m 3.1	m 2.4	m 1.6	m 2.4	m 6.30		m 1.8			10.3	d 1.10			
101	m 2.80	brs 1.10	brs 1.42	m 1.40	m 6.10		m 1.70	m 3.30	brs 2.3		d 1.10			
102	m 2.80	m 1.30	brs 1.40	brs 2.32	m 5.90		m 1.80	dxq 3.70			d 1.10	d 7.75	d 7.35	 2.44
103	m 2.80	m 2.0	brs 1.50	brs 2.30	m 6.15		m 1.80	m 2.30			d 1.10			
100	m 2.80	m 2.0	m 1.80	brs 2.40	m 6.10		m 1.70	m 2.20		brs 9.63	d 1.08			
97	m 3.30	overlapping m 3.20			m 6.30		m 1.70			brs 9.8	m 7.20			
106	m 2.90	overlapping m m 2.10		m 2.90	m 6.15		m 1.60	dxq 3.50	brs 2.90		m 7.20			
107	m 2.90	m 2.0	brs 2.40	m 2.90	m 6.10		m 1.52	dxq 4.0			m 7.15	d 7.75	d 7.35	 2.44
108	m 2.75	m 2.25	brs 2.40	m 3.0	m 6.25		m 1.70	m 2.25			m 7.20			
105	m 2.60	m 2.10	brs 2.80	brs 2.98	m 6.20		m 1.65	dxq 2.35			m 7.20			

2.1.3.0. Synthesis of norborn-5-en-2-ylbutanoic acid (116).

2.1.3.1. Preparation of the dienophile hex-5-enoic acid (112).

Scheme 4



(i) Py; (ii) Na; (iii) H_2O; (iv) PBr_3; (v) Mg; (vi) CO_2.

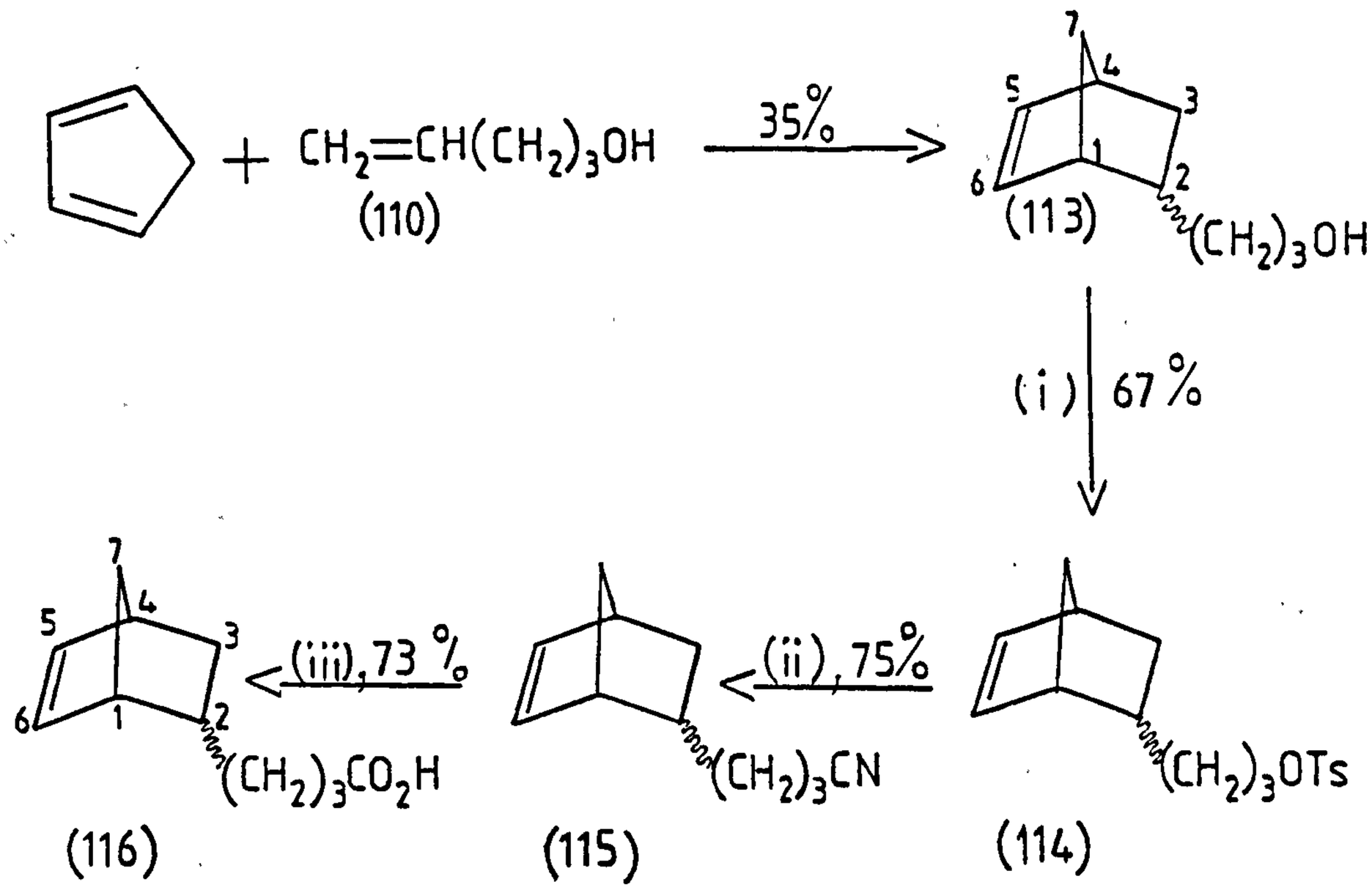
The required dienophile hex-5-enoic acid which should give the adduct (116) with cyclopentadiene was prepared as in Scheme 4.

Tetrahydrofurfuryl chloride (109) was obtained, from the reaction of tetrahydrofurfuryl alcohol and thionyl chloride in the presence of pyridine,[106] as a colourless liquid, b.p. 47-48° at 15 mm Hg (Lit.[106] b.p. 41-42° at 11 mm Hg). Treatment of the chloride (109) with powdered sodium in ether and subsequent decomposition by ice water gave pent-4-en-1-ol (110) as a colourless liquid, b.p. 42-43° at 110 mm Hg. (Lit. [106] b.p. 134-137° at Natm.).

The product alcohol (110) in the ir exhibited a medium absorption at 3500 cm^{-1} (OH) and the ^1H nmr showed a doublet of sextets at δ5.80 (H-4), a m at δ5.0 (H-5) and a sharp t at δ3.65 (-$\underline{CH_2}$-O-) with a brs at δ2.0 ($\underline{OH}$). The alcohol (110), on treatment with phosphorus tribromide[107] in the presence of pyridine was readily converted to 1-bromopent-4-ene (111) as a colourless liquid b.p. 130° at 760 mm Hg. (Lit.[107] b.p. 130° at 760 mm Hg). The ^1H nmr contained a doublet of sextets at δ5.80 (H-4), a m at δ5.0 (H-5) and a t at δ3.30 (-$\underline{CH_2}$-Br).

Using the standard procedure[126] the Grignard reagent pent-4-enylmagnesium bromide was prepared by the dropwise addition of 1-bromopent-4-ene to magnesium turnings in anhydrous ether at 0°. Treatment of the ethereal solution of Grignard reagent with small pieces of dry ice, followed by dilution with water and acidification, gave the required hex-5-enoic acid (112) as a colourless liquid, b.p. 103-105° at (13 mm Hg). (Lit.[108] b.p. 101-102° at 8 mm Hg). The ^1H nmr spectrum showed a s at δ11.38 (COO$\underline{H}$), two sextets at δ5.80 (H-5), a m at δ5.0 (H-6) and overlapping m at δ1.5-2.5 (2H-4, and 2H-3) protons. Unfortunately when a mixture of hex-5-enoic (112) and cyclopentadiene was heated in a sealed tube at 180° for 30 h, the only recognisable material was unchanged acid (112) together with polymeric material.

2.1.3.2. Scheme 5



(i) TsCl—Py ; (ii) KCN—DMSO ; (iii) KOH, H^+.

The unsuccessful attempt to obtain the acid (116) by the Diels-Alder addition of cyclopentadiene to hex-5-enoic acid (112), led to the alternative route using the alcohol (110) to give the adduct (113) on Diels-Alder addition with cyclopentadiene. The required acid (116) could then be obtained by extension of alcohol side chain as in Scheme 5.

Fortunately, the Diels-Alder addition of cyclopentadiene with pent-4-ene-1-ol (110) when the reactants were heated in a sealed tube at 180° for 60 h, followed by distillation, gave norborn-5-en-2-ylpropanol (113) in 35% yield as a colourless viscous liquid, b.p. 79-80° at 0.08 mm Hg.

The ir exhibited a medium absorption at 3500 cm^{-1} (OH) and the ^1H nmr showed a m at δ6.0 (olefinic protons in norbornene ring), a brs at δ3.85 (O<u>H</u>), a t at δ3.50 ($>CH_2$-O-) and a m at δ0.5 (H-3-<u>endo</u>) which were consistent with the structure of alcohol (113). The alcohol (113) also gave a correct molecular ion, m/e 152, in the mass spectrum.

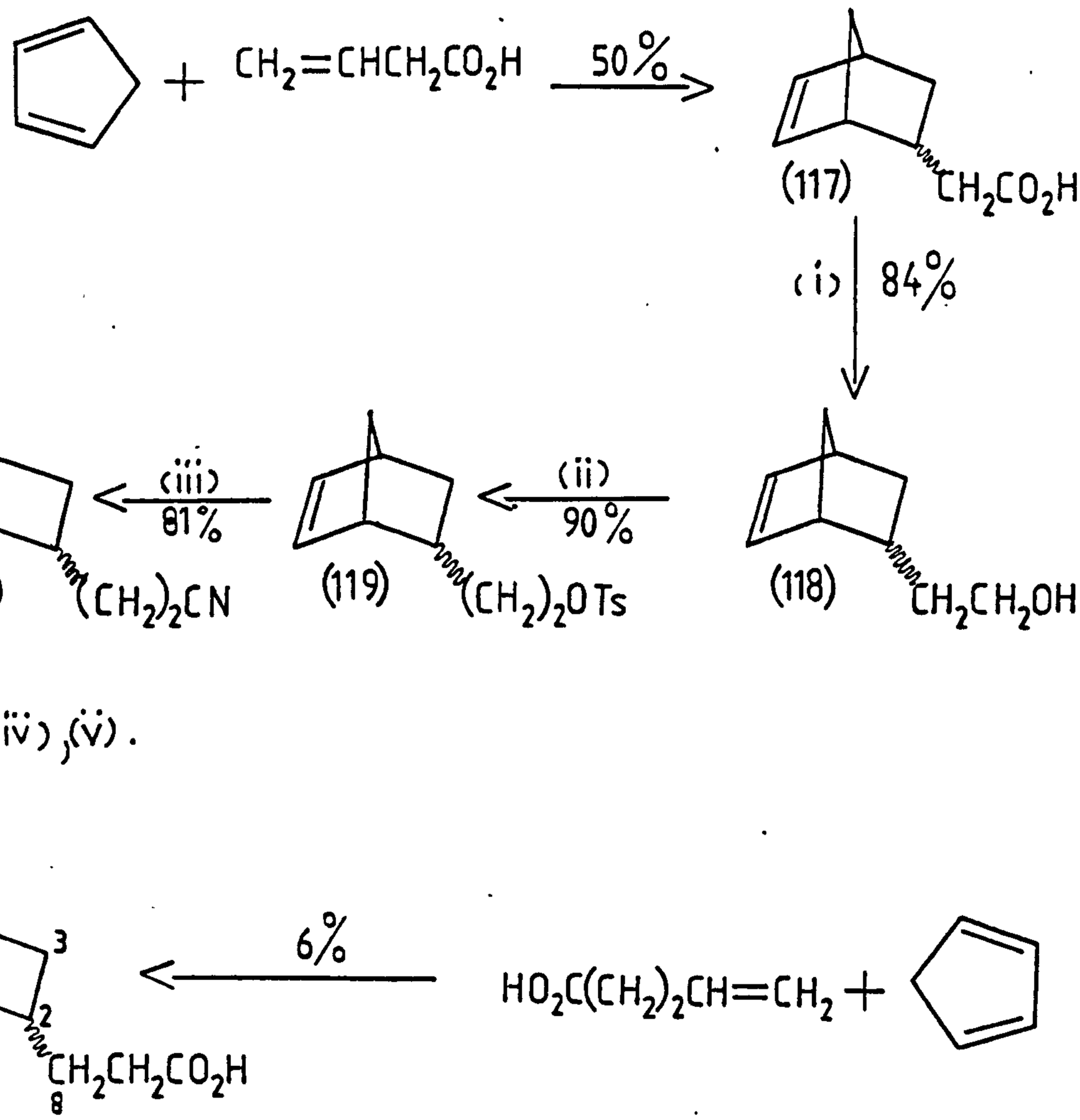
Tosylation of the resultant alcohol (113) with tosyl chloride in pyridine; the reaction mixture being kept in a refrigerator for 16 h, gave the corresponding tosylate (114). The structure of (114) was supported by the ^1H nmr spectrum which showed two d at δ7.80 and δ7.30 (<u>ortho</u>- and <u>meta</u>-protons) with J(<u>ortho</u>, <u>meta</u>) = 8 Hz, a m at δ6.0 (olefinic protons), a t at δ4.0 ($>C\underline{H_2}$-O-), a s at δ2.45 (p-$C\underline{H_3}$) and a m at δ0.5 (H-3-<u>endo</u>). Treatment of the tosylate (114) with potassium cyanide in DMSO as a solvent at 100° for 16 h gave the nitrile (115) in 75% yield). A medium absorption at 2250 cm^{-1} (-C≡N) which is usually found in nitriles was clearly seen in the ir spectrum of (115). Base hydrolysis with 10% aqueous potassium hydroxide by heating at 110° for 60 h, followed with acidification and extraction gave the required acid (116) in 73% yield. The acid (116) has a b.p. 122-123° at 0.3 mm Hg, and exhibited a medium broad absorption at 3300-2500 cm^{-1} (COO<u>H</u>) and a strong absorption at 1710 cm^{-1} (C = O of COOH) in the ir spectrum. The ^1H nmr showed a s at δ11.55 (COO<u>H</u>) a multiplet at δ6.0 of (olefinic protons), a broad resonance at δ2.75 integrating for two protons of H-1 and H-4, and high field protons at δ2.10-0.5.

TABLE 3. ^{1}H nmr data of compound involved in the formation of the acid (116).

Compound	δ (ppm)									
	H-1, H-4	H-2,H-3-exo,H-7 H-8 and H-9	$-CH_2-O$	H-5, H-6	H-3-endo	OH	COOH	ortho	meta	p-CH_3
113	m 2.75	overlapping m 2.5-0.8	t 3.50	m 6.0	dxm 0.5	s 3.85				
114	m 2.75	overlapping m 2.2-0.9	t 4.0	m 6.0	dxm 0.5			d 7.80	d 7.30	s 2.45
115	m	overlapping m 2.0-0.8	t 2.25	m 6.1	dxm 0.5					
116	m 2.75	overlapping m 2.10-1.0	t 2.30	m 6.0	dxm 0.5		s 11.55			

2.1.4.0. Synthesis of norborn-5-en-2-ylpropionic acid (121)

2.1.4.1. Scheme 6



(i) $LiAlH_4$; (ii) TsCl–Py ; (iii) KCN–DMSO ; (iv) KOH ; (v) H^+.

The Diels-Alder Reaction of cyclopentadiene and pent-4-enoic acid to give norborn-5-en-2-ylpropionic acid (121) was recently reported by Davies and Dowle[93] who obtained about 6% yield of acid (121). Scheme 6 shows the outline of an improved procedure for the synthesis of acid (121) by the extension of the carboxylic acid side

chain of norborn-5-en-2-ylacetic acid (117). The acid (117) is easily obtained from the Diels-Alder Reaction of cyclopentadiene and vinylacetic acid[109] by heating in a sealed tube at 180° for 8 h.

Reduction of the resultant acid (117) with lithium aluminum hydride gave the corresponding norborn-5-en-2-ylethanol (118) in 84% yield. The ir spectrum exhibited a medium absorption at 3500 cm^{-1} (OH), and the ^1H nmr clearly showed a brs at δ4.10 (OH), a t at δ3.50 ($>CH_2$-O-) with a m at δ6.0 of olefinic protons still present. Treatment of the alcohol (118) with tosyl chloride in pyridine, the reaction mixture being kept in the refrigerator for 16 h, gave norborn-5-en-2-ylethyl tosylate (119) in 90% yield.

Nucleophilic displacement of the tosylate group in (119), by the stronger nucleophile cyanide ion, is favoured on heating the tosylate with potassium cyanide in DMSO at 100° for 16 h and afforded the nitrile (120) in 81% yield. Hydrolysis of the nitrile (120) with 10% aqueous potassium hydroxide, followed by acidification and extraction, gave norborn-5-en-2-ylpropionic acid (121) in 83% yield. The acid (121) obtained has a b.p. 115-117° at 0.3 mm Hg; (Lit.[93] b.p. 102-103° at 0.05 mm Hg). The mass spectral data exhibited a molecular ion; m/e 166 which further confirmed the structure of acid (121).

TABLE 4. Summary ^{1}H nmr data of (118) - (121)

Compound	δ (ppm)									
	H-1, H-4	H-2,H-3-exo, H-7,H-8	$-CH_2-O-$	H-5, H-6	H-3-endo	OH	COOH	ortho	meta	p-CH_3
	m	m	t	m	dxd	s				
118	2.72	2.0-0.8	3.50	6.0	0.5	4.10				
	m	m	t	m	dxd			d	d	s
119	2.70	1.95-0.8	3.92	5.95	0.45			7.75	7.30	2.43
	m	m	t	m	dxd					
120	2.72	2.0-0.8	2.30	6.10	0.5					
	m	m	t	m	dxd		s			
121	2.78	1.95-0.9	2.35	6.08	0.5		11.0			

2.1.5.0. Summary

The Diels-Alder addition of cyclopentadiene and unsaturated acids is dependent on, (1) the relative positions of the double bond and carboxyl group, and (ii) the degree of substitution of the carbon-carbon double bond.

Unsubstituted α,β- unsaturated acids react more easily to give the adduct with cyclopentadiene and in a better yield, than for the α,β- unsaturated acids. An example is a comparison between acrylic acid and trans-crotonic acid.

Cyclopentadiene and acrylic acid gave the acid adduct (91) in 62.5% yield on heating at 60° for 3 h, while trans-crotonic acid with cyclopentadiene simply afforded the acid adduct (96) in 20.3% yield in refluxing for 4 h. The effect of the alkyl substituent becomes more obvious in the β,γ- unsaturated acid. Vinylacetic acid gave the acid adduct (117) in about 50% yield with cyclopentadiene, but in contrast pent-3-enoic acid (98) and 4-phenylbut-3-enoic acid (104) do not give the respective acids (100) and (105) under comparable conditions.

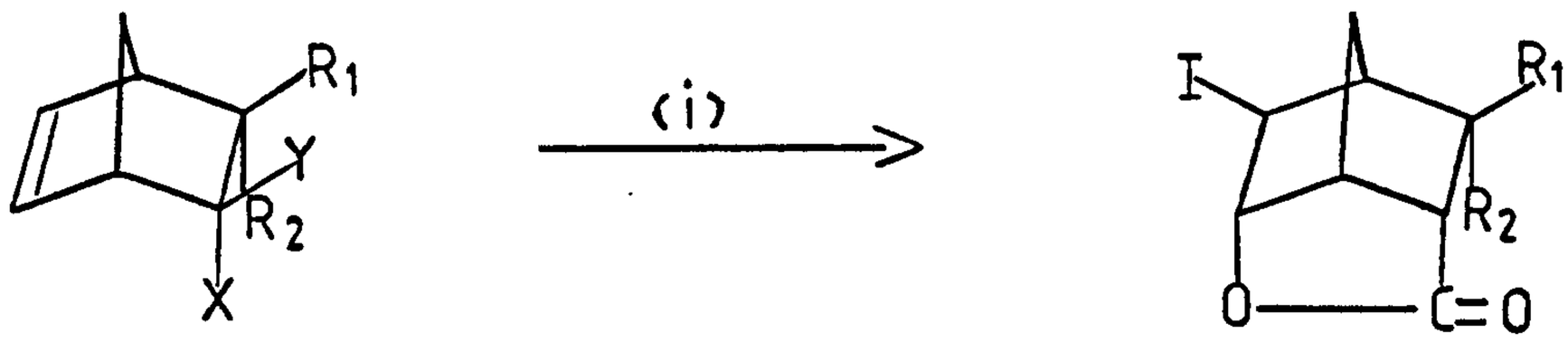
The question for the preparation of norborn-5-en-2-yl derivative of carboxylic acids with a longer side chain is answered by the extension of the carboxylic acid side chain which is the product from the Diels-Alder addition of cyclopentadiene with α,β- or β,γ- unsaturated acids. Reduction of the carboxylic acid group to alcohol, followed with tosylation to tosylate, nucleophilic

displacement with cyanide, and subsequent hydrolysis of the resultant nitrile gives the required acids in reasonable yield.

An example, 3-phenylnorborn-5-en-2-ylacetic acid (105) was obtained in overall yield of 20% corresponding to the starting dienophile of trans-cinnamoyl chloride with cyclopentadiene.

2.2.0.0. Iodolactonisation of norborn-5-en-2-endo-ylcarboxylic acid derivatives.

2.2.1.0. Scheme 7



(91a) $R_1, R_2, Y = H$; $X = CO_2H$.

(91b) $R_1, R_2, X = H$; $Y = CO_2H$.

(96a) $R_1 = Me$; $R_2, Y = H$; $X = CO_2H$.

(96b) $R_1, X = H$; $R_2 = Me$; $Y = CO_2H$.

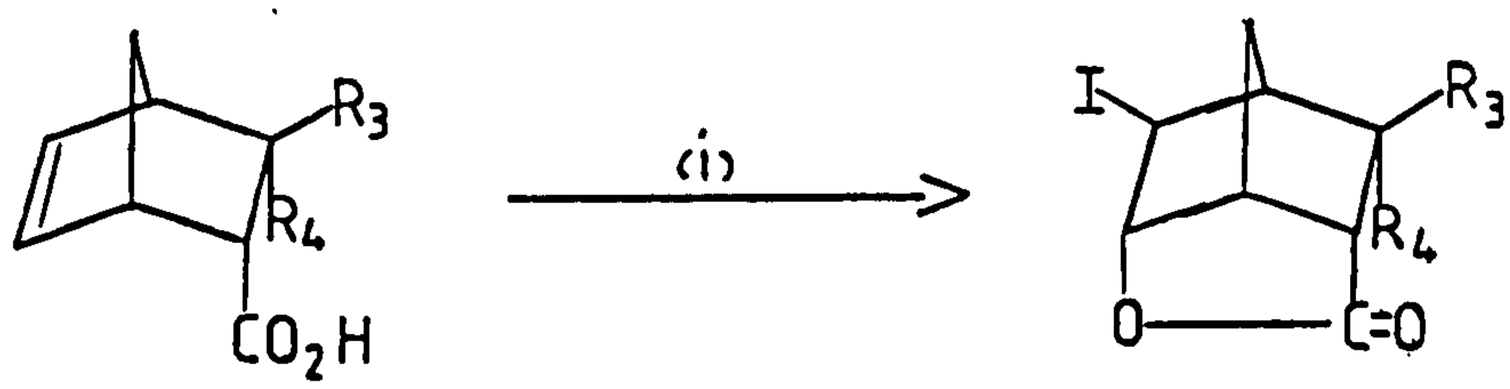
(97a) $R_1 = Ph$; $R_2, Y = H$; $X = CO_2H$.

(97b) $R_1, X = H$; $R_2 = Ph$; $Y = CO_2H$.

(122) $R_1, R_2 = H$.

(127) $R_1 = Me$; $R_2 = H$.

(128) $R_1 = Ph$; $R_2 = H$.



(93) R_3=H; R_4=CO_2H.
(94) R_3=H; R_4=CO_2Me.
(95) R_3=CO_2H; R_4=H.

(123) R_3=H; R_4=CO_2H.
(124) R_3=H; R_4=CO_2Me.
(125) R_3=CO_2H; R_4=H.
(126) R_3=CO_2Me; R_4=H.

(i) 0·5N $NaHCO_3$, I_2, KI.

2.2.1.1. The norborn-5-en-2-ylcarboxylic acid derivatives obtained from the Diels-Alder addition of cyclopentadiene to unsaturated acids consist of a mixture of <u>endo</u> and <u>exo</u> acid isomers. When this mixture of acids was subjected to iodolactonisation under standard conditions by reaction with iodine and potassium iodide in 0.5N aqueous sodium bicarbonate at 5^{o} for 0.5 h and then in the dark at room temperature for 16 h, iodolactone is produced solely from the <u>endo</u>-isomer. The <u>exo</u>-acid isomer remains in the alkaline solution either in the form of the sodium salt or is converted to the iodohydrin by the addition of positive iodine and hydroxyl anion to the double bond, a product which also remains in solution as the sodium salt.

In most cases the <u>exo</u>-acid isomer is largely converted into an iodohydrin; 3-<u>endo</u>-phenylnorborn-5-en-2-<u>exo</u>-ylcarboxylic acid (97b), was the only acid obtained in a good yield on acidification of the alkaline solution following

the iodolactonisation reaction on a mixture of endo and exo-acids (97).[97]

2.2.1.2. The iodolactonisation of norborn-5-en-2-endo-ylcarboxylic acid (91a) affords the iodo-γ-lactone (122). The reaction and the structure of the lactone (122) is well established.[116-118] Iodolactonisation of the acid (91) , a mixture of endo-acid (91a) and exo-acid (91b) under standard conditions gave the identical iodo-γ-lactone (122) in 60.4% yield.

The same iodolactonisation of norborn-5-en-2-endo, 3-endo-yldicarboxylic acid (93), norborn-5-en-3-endo-carbomethoxy-2-endo-ylcarboxylic acid (94), norborn-5-en-2-endo, 3-exo-yldicarboxylic acid (95), 3-methylnorborn-5-en-2-ylcarboxylic acid (96) and 3-phenylnorborn-5-en-2-ylcarboxylic acid (97) afforded the iodo-γ-lactones (123),[121] (124),[120] (125), (127),[102] and (128)[97] in yields of 53%, 76%, 73%, 79%, and 79% respectively.

Methylation of the carboxyl group of the acidic iodo-γ-lactones (123) and (125) with cold diazomethane in ether gave the corresponding methyl ester iodo-γ-lactones (124) and (126) respectively.

TABLE 5. Summary of the product and % yield of the iodo-γ-lactone

Compound	Reaction Condition	Product	% Yield	Literature		
				Reaction Condition	% Yield	Ref.
91	(i)	122	60	(iii)	42	116
93		123	53	(iii)	-	121
94		124	76	(iv)	26	120
95		125	73	(iii)	-	121
96		127	79	(i)	85	102
97		128	79	(iii)	30	97
123	(ii)	124	90			
125		126	91			

(i) Iodolactonisation under standard condition

(ii) Treatment with cold diazomethane

(iii) The acid is dissolved in 10% aqueous sodium hydroxide and sodium bicarbonate, then treated with a solution of iodine and left for 16 h.

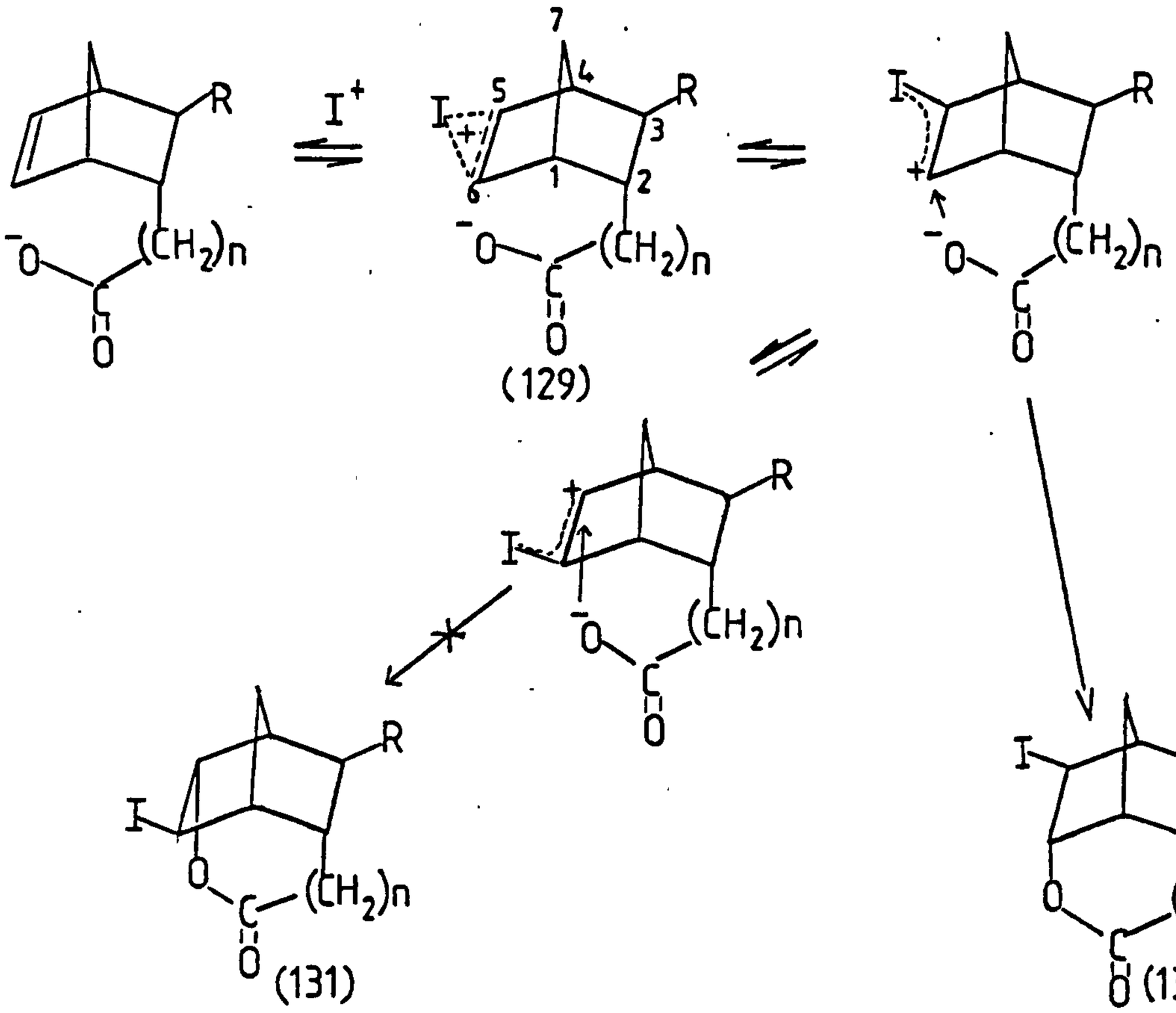
(iv) 1 N aqueous sodium bicarbonate to dissolve the acid and treated with a solution of iodine and potassium iodide and left for 16 h.

The type of the inorganic base used effects the yield of the product iodolactone. Excess of sodium hydroxide[123-125] and sodium carbonate[3] leads to a decrease in the yield of the iodolactone. It seems that 0.5 N aqueous sodium bicarbonate is the best choice and leads to the satisfactory yields of the iodo-γ-lactones reported in Table 5.

The product iodo-γ-lactones could be easily recognised from their ir spectra. All the iodo-γ-lactones (122) - (128) gave a strong absorption at around 1760-1780 cm^{-1}, which is characteristic of a γ-lactone.[122] The ^1H nmr spectrum showed a complete loss of the olefinic protons at δ6.0 in the starting acids and the appearance of two new low field peaks in the region δ5.10 (>C<u>H</u>-O-) and δ4.3 (>C<u>H</u>-I).

The reaction mechanism given in Scheme 8 follows the earlier proposals by van Tamelen and Shamma,[5] and involves the <u>exo</u> attack of positive iodine to the carbon-carbon double bond of the 2-<u>endo</u> acid isomer leading to the iodonium ion intermediate (129).

Scheme 8



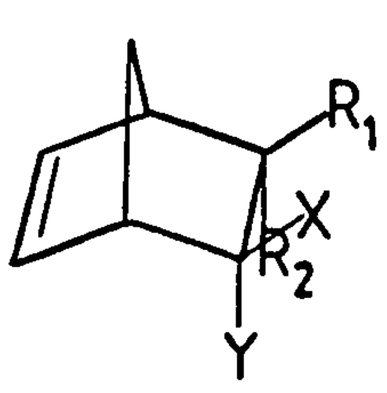
Subsequent intramolecular capture of the iodonium ion centre in (129) by the carboxylate anion is favoured at C-6 rather than at C-5. This is because of the closer proximity of the carbocation centre at C-6 to the carboxylate anion centre which leads to the thermodynamically more stable product. In the case n = 0, the iodo-γ-lactone (130) is a sole product.

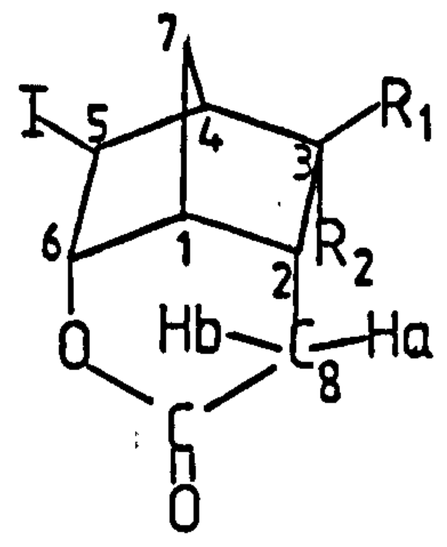
TABLE 6. ^{1}H nmr data of the iodo-γ-lactones (122)-(128).

Compounds	δ (ppm)								
		2-exo	3-exo	3-endo	4	5-endo	6-exo	7-anti	7-syn
122	brt 3.2	m 2.50	m 2.08	m 1.90	m 2.7	d 3.85	d 5.10	m 2.35	m 1.70
123	m 3.28	q 2.80	q 3.17	brs 10.3	m 2.89	d 4.60	d 5.18	brd 2.44	brd 1.91
124	m 3.31	q 2.80	q 3.11	s 3.72	m 2.89	d 4.62	d 5.10	dxt 2.44	dxq 1.89
125	m 3.24	m 2.99	brs 5.18	m 2.99	brs 2.92	d 4.05	d 5.10	q 2.32	brd 1.89
126	m 3.12	m 3.12	s 3.71	m 3.12	m 2.83	d 3.88	d 5.10	dxt 2.30	brd 1.95
127	t 3.10	m 2.10	d 1.10	m 2.12	brs 2.42	d 3.85	d 5.10	m 2.30	m 2.15
128	m 3.30	m 2.90	m 7.20	m 2.90	m 3.30	d 4.04	d 5.20	m 2.90	

2.2.2.0. Iodolactonisation of 3-methylnorborn-5-en-2-ylacetic acid (100) and 3-phenylnorborn-5-en-2-ylacetic acid (105).

2.2.2.1. Scheme 9





(117a) $R_1, R_2, X = H$; $Y = CH_2COOH$.

(117b) $R_1, R_2, Y = H$; $X = CH_2COOH$.

(132) $R_1; R_2 = H$.

(133) $R_1 = CH_3; R_2 = H$.

(134) $R_1 = C_6H_5; R_2 = H$.

(100a) $R_1 = CH_3, R_2, X = 4$; $Y = CH_2$-COOH.

(100b) $R_1, Y = H; R_2 = CH_3$; $X = CH_2COOH$.

(105a) $R_1 = C_6H_5, R_2, X = H$; $Y = CH_2COOH$.

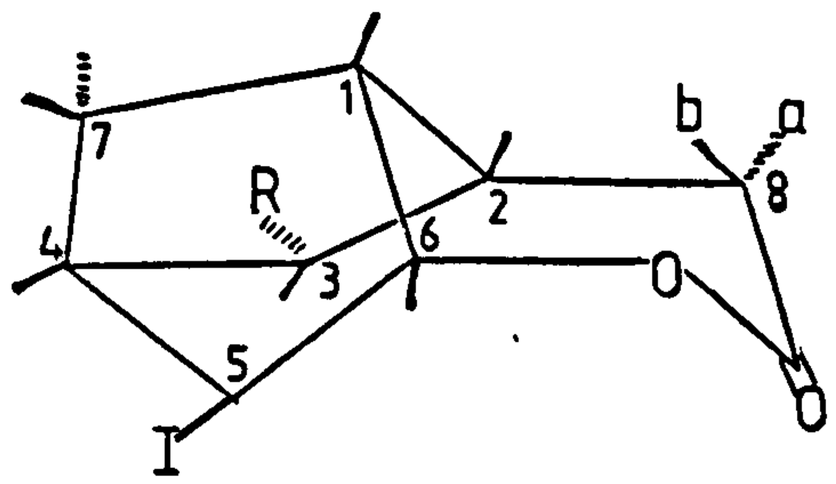
(105b) $R_1, Y = H; R_2 = C_6H_5$; $X = CH_2COOH$.

(i) 0.5N $NaHCO_3$, I_2, KI.

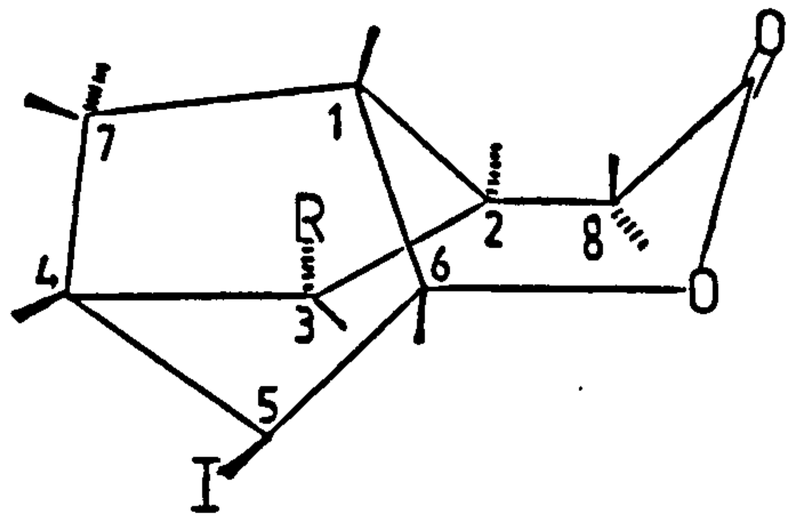
2.2.2.2. The iodolactonisation of the acid (117) [a mixture of endo acid (117a) and exo acid (117b)] to afford the iodoδ-lactone (132) is well documented, and the structure of the iodoδ-lactone (132) is reported to contain a boat conformation[93] of the lactone ring.

Treatment of the acid (100) [a mixture of endo isomer (100a) and its exo isomer (100b)] and the acid (105) [a mixture of endo-isomer (105a) and its exo isomer (105b)] with a solution of iodine and potassium iodide under the standard procedure gave the corresponding iodo δ -lactones (133) and (134) in yields of 53% and 71% respectively. The iodoδ-lactones (133) and (134) exhibited a respective strong absorption at 1730 cm^{-1} and 1735 cm^{-1} in the infrared ; (a characteristic of $\rangle C=O$ in a δ-lactone).

The ^1H nmr of iodoδ-lactone (133) in solvent $CDCl_3$ shows a m at δ5.24 ($\rangle$CH-O -) , a q at δ3.85($\rangle$CH-I), a d at δ2.62 (H-8a, H-8b), a m at δ2.38 (H-1), a brs at δ2.24 (H-4), and a d at δ1.10 of CH_3 which are consistent with the structure (133). A d at δ2.62 of H-8a, H-8b [J(8,2-exo) = 4 Hz] indicates that both protons H-8a and H-8b are equivalent, and the observed coupling constant of 4 Hz shows the lactone ring of iodoδ-lactone (133) contains a chair conformation (133A). This assumption is based on the Karplus equation[127] which shows coupling constants of (7 and 1 Hz) for J(2-exo,8a) and J(2-exo,8b) respectively for boat conformation (133B), and a value of (3 and 3 Hz) for the alternative chair conformation (133A). The chair conformation is further supported by the deshielding effect due to the anisotropy of the carbonyl function on H-1 which shows a lower field chemical shift compared to that of the H-2-exo protons.



(133A) R = Me
(134A) R = Ph



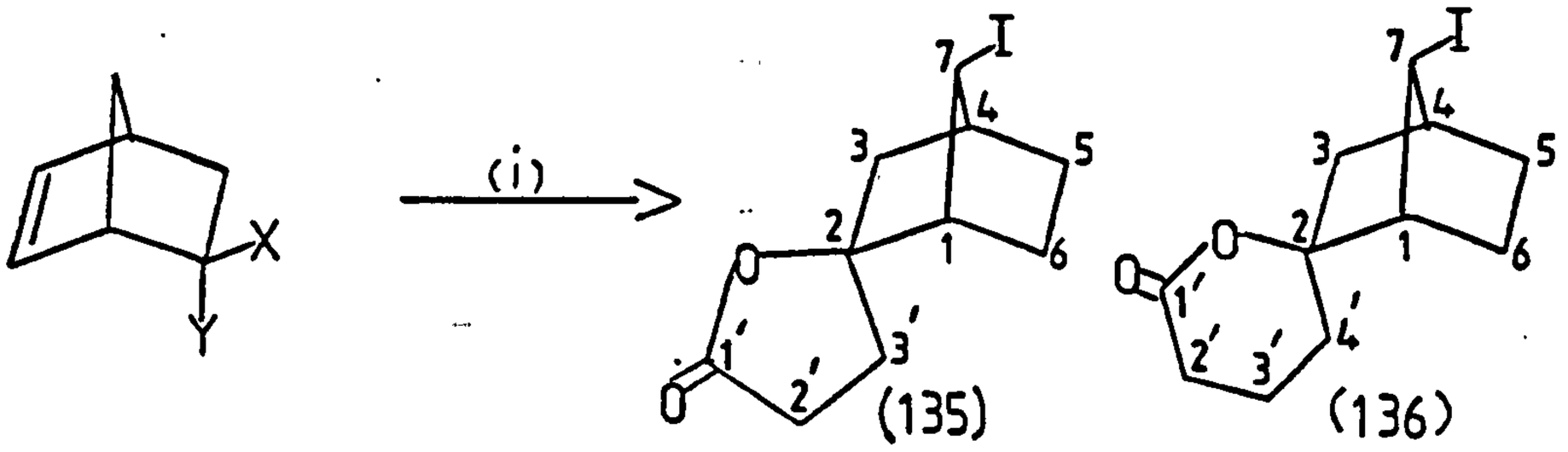
(133B) R = Me
(134B) R = Ph

The two protons H-8a and H-8b which should be non-equivalent are clearly seen in the ^{1}H nmr using C_6D_6 as a solvent, which gives a q at δ2.20 (H-8b) and a q at δ2.0 (H-8a) with J(8b,2-exo) = 3 Hz, J(8a,2-exo) = 5 Hz and J8a,8b = 18 Hz. The coupling constants of 5 and 3 Hz for J(8a,2-exo) and J(8b,2-exo) respectively, further indicate the lactone ring of the iodoδ-lactone (133), although not a perfect chair is much closer to a chair conformation rather than a boat conformation. The ^{1}H nmr of the iodoδ-lactone (134) in $CDCl_3$ as solvent shows a brd at δ5.33 (>CH-O-), a t at δ4.0 (>CH-I), a d at δ2.73 (H-8a, H-8b), a m at δ2.53 (H-1, H-4, H-2-exo) and a q x m at δ2.25 (H-7anti, H-7syn). The d at δ2.73 with a coupling constant of 3 Hz corresponds to J(8,2-exo) and shows that the protons H-8a and H-8b are equivalent in solvent $CDCl_3$. The value of coupling constants J(8,2-exo) = 3 Hz which is equivalent to the Karplus equation for a chair conformation, then strongly indicated that the lactone ring (134A) of the iodoδ-lactone (134) contains a chair conformation. The presence of respective methyl and

phenyl substituents at the C-3 position in the iodo δ-lactones (133) and (134) causes the lactone ring to tend towards a chair conformation rather than a boat conformation as found in unsubstituted iodoδ-lactone (132).[93]

2.2.3.0. Iodolactonisation of norborn-5-en-2-ylpropionic acid (121) and norborn-5-en-2-ylbutanoic acid (116).

2.2.3.1. Scheme 10



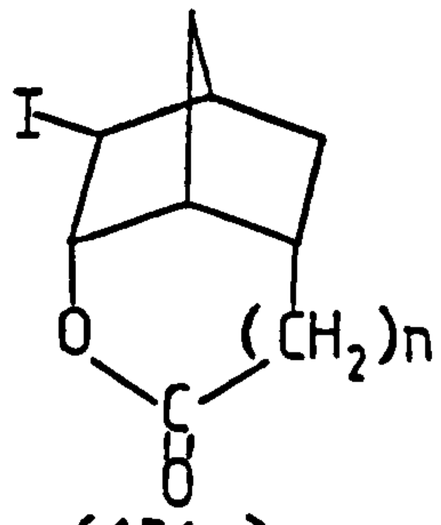
(116a) X = H; Y = $-(CH_2)_3CO_2H$.

(116b) X = $-(CH_2)_3CO_2H$; Y = H.

(121a) X = H; Y = $-(CH_2)_2CO_2H$.

(121b) X = $-(CH_2)_2CO_2H$; Y = H.

(i) I_2, KI, $NaHCO_3$.



(136a)

2.2.3.2. Iodolactonisation of norborn-5-en-2-endo-ylcarboxylic acid (91a) and norborn-5-en-2-endo-ylacetic acid (117a) give the corresponding iodoγ-lactone (122) and iodoδ-lactone (132) respectively. Davies and Dowle[93] found that iodolactonisation of norborn-5-en-2-ylpropionic acid (121) [a mixture of endo-acid isomer (121a) and its exo-acid isomer (121b)] did not give the corresponding iodoε-lactone (136a), n = 2; instead the product was the spiroγ-lactone (135). A repeat of this iodolactonisation

TABLE 7. ^{1}H nmr data of the iodoδ-lactones (133) - (134)

Compound	Solvent	δ (ppm) 1	2-exo	3-exo	3-endo	4	5-endo	6-exo	7-anti	7-syn	8a	8b
133	$CDCl_3$	m 2.38	m 1.96	d 1.10	m 1.34	m 2.24	q 3.85	m 5.24	q 1.80	m 2.10	d 2.62	
133	C_6D_6	m 1.71	m 1.71	d 0.52	m 0.79	m 1.71	q 3.54	brt 4.97	m 1.13	m 1.27	q 2.20	q 2.0
134	$CDCl_3$	m 2.40	m 2.40	m 7.32	m 2.70	m 2.40	brt 4.0	d 5.33	dxm 2.18	brd 2.30	d 2.73	

reaction of norborn-5-en-2-ylpropionic acid (121) gave the same spiro-γ-lactone (135) in yield of 22%, m.p. 91-93°. (Lit.[93] yield of 45%; m.p. 92.5-96.5°). The ir spectra shows a strong absorption at 1770 cm^{-1} (>C= O of a γ-lactone) and the ^1H nmr contains only one low field peak, a brs at δ3.95, integrating for one proton due to >C<u>H</u>I at C-7. The remaining proton resonances overlap in the region δ1.40-2.6.

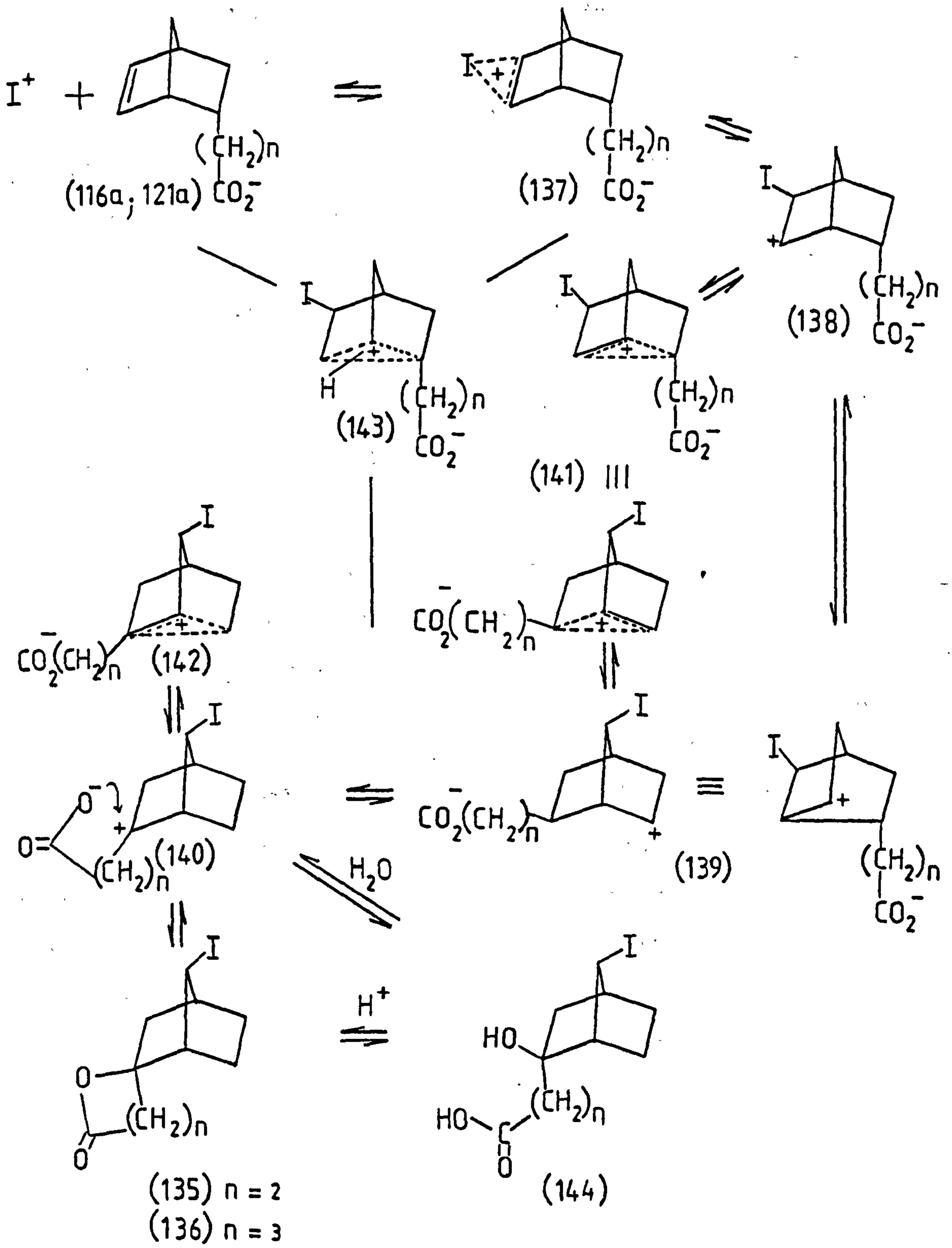
In an attempt to investigate further formation of spiro iodo-lactones from norborn-5-en-2-<u>endo</u>-ylcarboxylic acid derivatives with a longer side chain; norborn-5-en-2-ylbutanoic acid (116) [a mixture of <u>endo</u>-acid isomer (116a) and its <u>exo</u>-isomer (116b)] was subjected to iodolactonisation under standard condition. The product spiro δ-lactone was obtained in 20% yield by acidification of the alkaline reaction mixture, and not from the neutral fraction prior to acidification.

The product (136) showed a strong absorption at 1735 cm^{-1} (>C=O of a δ-lactone), and further support was gained from the mass spectrum which exhibited a molecular ion m/e 306.

The spiro iodoδ-lactone (136) in the ^1H nmr gave no indication of a >C<u>H</u>O resonance; the sole low field resonance is a brs at δ4.47 due to >C<u>H</u>I. The remaining protons shown give rise to an overlapping m at δ2.44-1.22 integrating for 14 protons.

The ^{13}C nmr shows two singlets at δ170.4 and δ88.30 due to the C-1' and C-2 respectively, and provide further evidence of the structure of spiro iodoδ-lactone (136).

Scheme 11



A likely mechanism for the formation of (136) is indicated in Scheme 11. The mechanism is based on that proposed earlier for the formation of the spiro iodo-γ-lactone (135).[93] The attack of the positive iodine on the carbon-carbon double bond of (121a) and (116a) gives the iodonium ion (137). Because capture of the iodonium ion (137) by the carboxylate anion to form 7-membered (n = 2) and 8-membered (n = 3) lactones is slow for steric reasons, the open carbocation (138) derived from (137) is likely to undergo Wagner-Meerwein rearrangement to afford (139). This appears to be the sole possible route for rearrangement of (138), since a 5,6-exo, exo or 2,6-endo, endo hydride shifts cannot be envisaged. (The tendency for 5,6-exo, exo, 2,6-endo, endo hydride shifts and Wagner-Meerwein rearrangement in norbornane systems has been reviewed).[64,82b]

The carbocation (139) would then undergo the favourable 2,6-endo, endo hydride shift to give the tertiary carbocation (140). Intramolecular cyclisation in (140) of the carboxylate anion centre on to the carbocation centre then occurs to afford the iodolactones (135) n = 2; and (136) n = 3. These are then hydrolysed spontaneously to the hydroxy acid (144). Alternatively, the tertiary carbocation centre in (140) is captured by a molecule of water to give (144) faster than the intramolecular cyclisation of the carboxylate anion. The hydroxy acid (144) in the presence of mineral acid is believed to undergo intramolecular dehydration to afford the observed spiro iodo-γ- and δ- lactones (135) and (136) respectively.

The assumption of exo-attack in (140) is based on the known high preference for exo-attack on tertiary norbornyl cations.[64,82b,77b]

Instead of the classical carbocations (138)-(140), product formation of the iodolactones (135) and (136) can also be considered via non-classical ions (141) - (142), for which (143) is a composite. In the non-classical ion theory, σ-bridging in the norbornyl cation has been considered the controlling factor stabilising the ion and leading to products derived from the exo-attack.[64,82b]

TABLE 8. Summary of the ^1H nmr data for iodolactones (135) and (136)

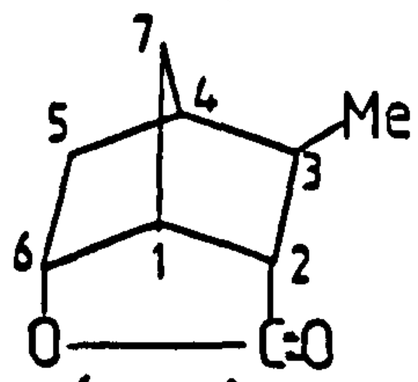
Compounds	δ (ppm)	
	H-7syn	Remaining protons
135	3.95	1.40 - 2.60
136	4.47	1.22 - 2.44

TABLE 9. Summary of the ^{13}C nmr data for iodolactone (136)

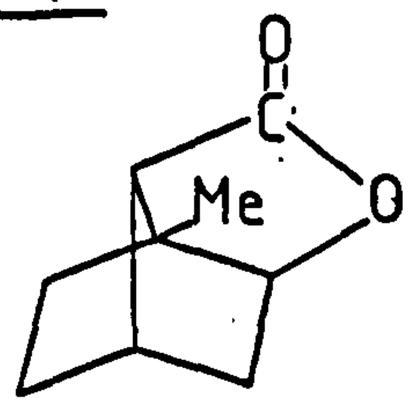
Carbon	δ (ppm)	Multiplicity
1	54.3	d
1'	170.4	s
2	88.3	s
2'	32.07	t
3	43.9	t
3'	17.0	t
4	44.7	d
4'	29.08	t
5	26.91	t
6	21.93	t
7	30.14	d

2.3.0.0. Acid catalysed lactonisation of norborn-5-en-2-ylcarboxylic acid derivatives.

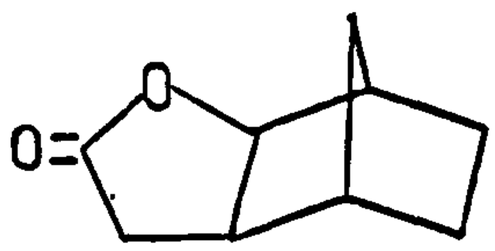
2.3.1.1. Scheme 12



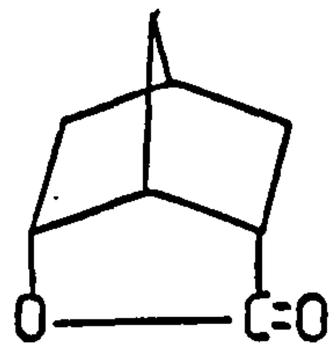
(146a)



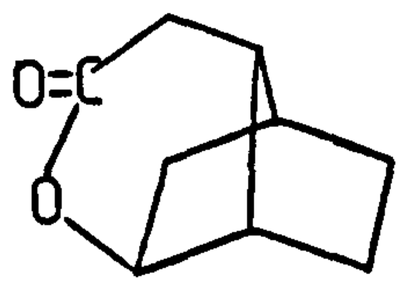
(146b)



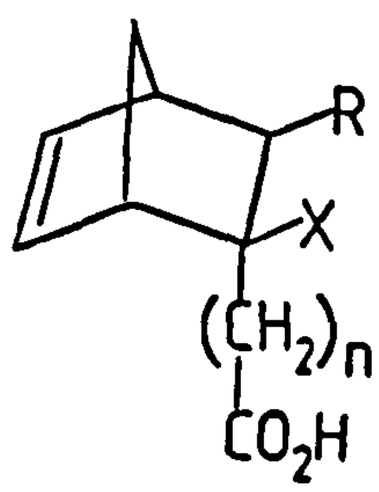
(147a)



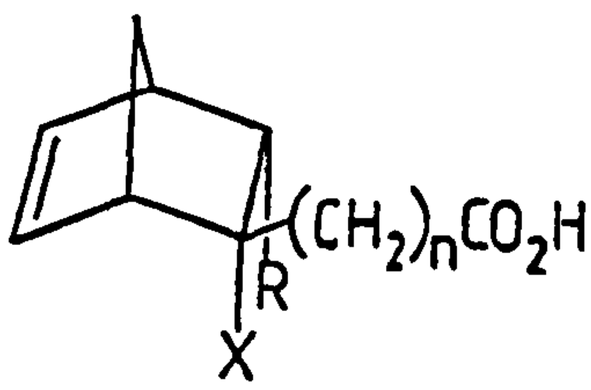
(145a)



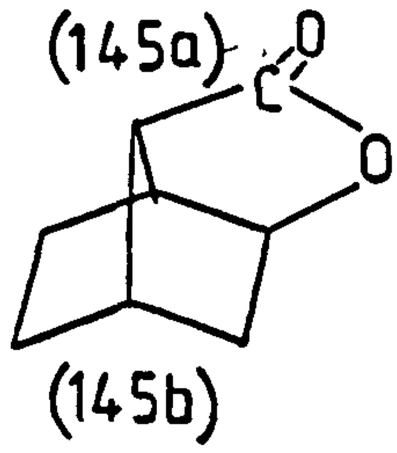
(147b)



91a; 96a;



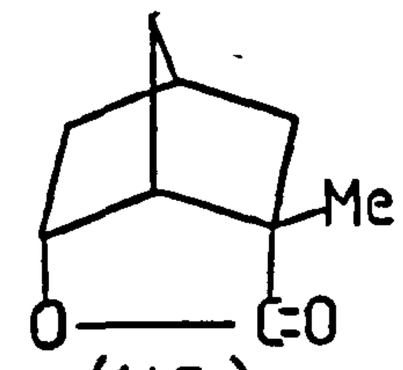
91b; 96b;



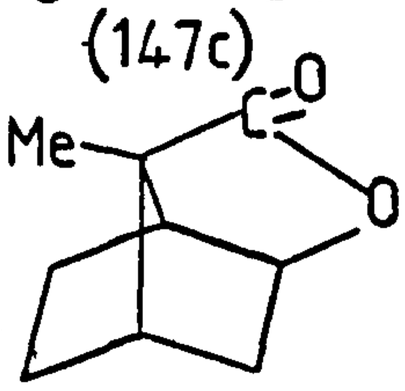
(145b)

116a; 117a; 116b; 117b;

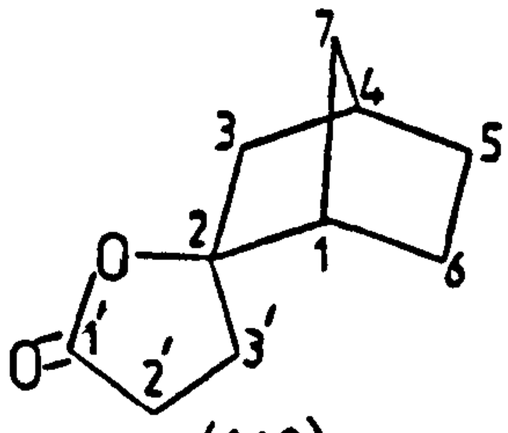
121a; 121c. 121b; 121d.



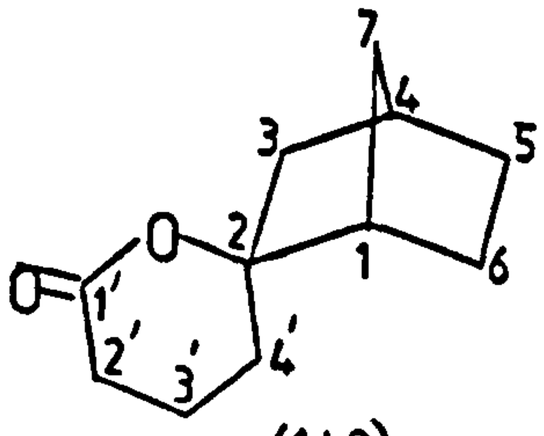
(147c)



(147d)



(148)



(149)

(91a — 91b) R, X = H ; n = 0.

(96a — 96b) R = Me, X = H; n = 0.

(116a — 116b) R, X = H ; n = 3.

(117a — 117b) R , X = H ; n = 1.

(121a — 121b) R, X = H ; n = 2.

(121c — 121d) R = H , X = Me , n = 0.

2.3.1.2. The readiness with which norborn-5-en-2-endo-ylcarboxylic acid derivatives form cyclic iodolactones has been discussed in the Section 2.2.0.0. The reaction has been accepted as the best method for the separation of endo and exo isomers of norbornene carboxylic acids. In comparison acid catalysed cyclisation affords a lactone or a mixture of lactones derived from both endo and exo isomers of norbornene carboxylic acid and cannot be used to separate the isomers.

Alder and Stein[95] reported that the acid catalysed cyclisation of norborn-5-en-2-endo-ylcarboxylic acid (91a) afforded the γ-lactone (145a). Later it was shown by Beckmann and Geiger[119] that when either the endo-acid (91a) or exo-acid (91b) were treated with 75% aqueous sulphuric acid, a mixture of the γ-lactones (145a) and (145b) was initially formed. On prolonged reaction times (240 h), only the γ-lactone (145a) was obtained as sole product.

Davies and Dowle[94] in their extension of the above observation found that norborn-5-en-2-ylacetic acid (117a) and (117b) on reaction with 50% aqueous sulphuric acid afforded a mixture of the γ-lactones (147a) and (147b). They further demonstrated that both of the γ-lactones (147a) and (147b) were formed when either norborn-5-en-2-ylacetic acid (117) [a mixture of endo-acid (117a) and its exo-acid (117b)], or the pure endo-acid (117a) were employed. The relative amounts of the lactones (147a) and (147b) were dependent on reaction times, with the amount of the γ-lactone (147) increasing with the longer reaction times indicating that it was thermodynamically the more stable

product. Beckmann and Geiger[119] also reported that the endo-acid isomer (121c) on reaction with 50% aqueous sulphuric acid for 2 days gave a mixture of the γ-lactones (147c) and (147d), with the amount of the γ-lactone (147d) increasing when 75% aqueous sulphuric acid was used under the same condition, indicating that it was the thermodynamically more stable product. The exo-acid isomer (121d) when subjected to reaction with 75% aqueous sulphuric acid for 18 h afforded only the γ-lactone (147d) as sole product. Recently Moriarty et al.[128] gave further proof of the structures of γ-lactones (147c) and (147d) by chemical degradation to 2,2-dimethylnorbornane and 7,7-dimethyl-norbornane respectively.

2.3.1.3. Treatment of 3-exo-methylnorborn-5-en-2-endo-ylcarboxylic acid (96a) [obtained from reduction of the iodoγ-lactone (127) with zinc in acetic acid[129]] with 50% aqueous sulphuric acid resulted in the formation of a mixture of the lactones (146a) and (146b). The product which was a mixture of the lactones (146a) and (146b) showed a strong absorption at 1765 cm^{-1} (>C = O of a γ-lactone). Based on the differences in chemical shift and coupling constants of the equivalent protons in the ^1H nmr spectra, the structure of the lactones (146a) and (146b) were readily determined. The >CH-O- proton at 6-exo in (146a) occurs as a brt at δ4.75 [J(1,6-exo) = J(5-exo, 6-exo) = 6 Hz]; in contrast the comparable proton at 3-endo in (146b) occurs at δ4.25 as a br m. This shift to higher field is consistent

with the general rule that endo protons occur at higher field than exo protons.[63] A d at δ1.10 [$J(CH_3, H\text{-}3endo) = 7$ Hz] of CH_3 at C-3 in (146a) and a s at δ1.25 for the CH_3 protons at the bridge head C-4 position in (146b) provides further evidence for the structures of the lactones (146a) and (146b). Separation of the mixture of lactones (146a) and (146b) did not prove possible either by column or preparative layer chromatography (p.l.c.); the relative amounts of the product lactones were therefore measured using gas liquid chromatography (g.l.c.) with a column of Carbowax 20M on Chromosorb W 80-100 mesh. At 170° the lactones (146b) and (146a) had retention times of 5.2 min and 7.4 min respectively.

A reference specimen of the lactone (146a) was obtained from the deiodination of the iodoγ-lactone (127) with tri-n-butyltin chloride[131] and sodium borohydride in ethanol. The resulting specimen of lactone (146a) showed a strong absorption at 1765 cm^{-1} (>C=O of a γ-lactone) in the infrared . The ^1H nmr spectrum showed the characteristic resonances at δ4.75 (brt), 3.10 (t), 1.10 (s) due to H-6-exo, H-1 and - CH_3 respectively that had previously been observed as due to (146a) in the spectrum of a mixture of (146a) and (146b). The relative amounts of the lactones (146a) and (146b) are reported in Table 12. They are very much less dependent on reaction time than proportion of the lactones derived from (91) and (117).

TABLE 12.

Compound	Time (h)	% Yield
146a	1	56
	3	50
	22	48
	90	48
146b	1	44
	3	50
	22	52
	90	52

The small differences in yield of the lactones (146a) and (146b) for the longer reaction times suggests that both of the γ-lactones (146a) and (146b) have comparable thermodynamic stability.

2.3.1.4. Norborn-5-en-2-ylpropionic acid (121) [a mixture of endo-acid (121a) and exo-acid (121b)] and norborn-5-en-2-ylbutanoic acid (116) [a mixture of endo-acid (116a) and exo-acid (116b)] on stirring with 50% sulphuric acid at room temperature for 22 h, were found to have been converted into the spiro γ-lactone (148) and the spiro δ-lactone (149) in yields of 80% and 79% respectively. The lactone (148) exhibited a strong absorption in the infrared at 1780 cm^{-1} (>C=O of a γ-lactone), whereas the lactone (149) gave a strong absorption at 1730 cm^{-1} (>C=O of a δ-lactone). Both of the lactones (148) and (149) in the ^1H nmr did not show a low field proton resonance corresponding to >C<u>H</u>-O; the spectrum composed solely

a high field overlapping m at δ2.80-1.20. The formation of the lactones (148) and (149) is believed to follow pathways similar to those involved in the iodolactonisation of the acids (121) and (116) to give the respective spiro iodoγ-lactone (135) and spiro iodoδ-lactone (136). The structure of the lactones (148) and (149) is further supported by the ^{13}C nmr for which the lactone (148) gave two singlets which resonated at δ176.67 and δ93.58 corresponding to C-1' and C-2 respectively. The lactone (149) also showed two singlets at δ171.4 and δ91.3 also due to C-1' and C-2. A summary of the ^{13}C nmr data for (148) and (149) is given in Table 13 below;

TABLE 13. ^{13}C nmr data for the lactones (148) and (149)

Compound	δ (ppm)										
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-1'	C-2'	C-3'	C-4'
148	d 46.38	s 93.58	t 29.73	d 45.67	t 22.22	t 28.02	t 30.60	s 176.67	t 36.40	t 37.93	
149	d 46.85	s 91.30	t 27.85	d 46.73	t 17.30	t 22.98	t 29.31	s 171.4	t 33.01	t 36.24	t 36.80

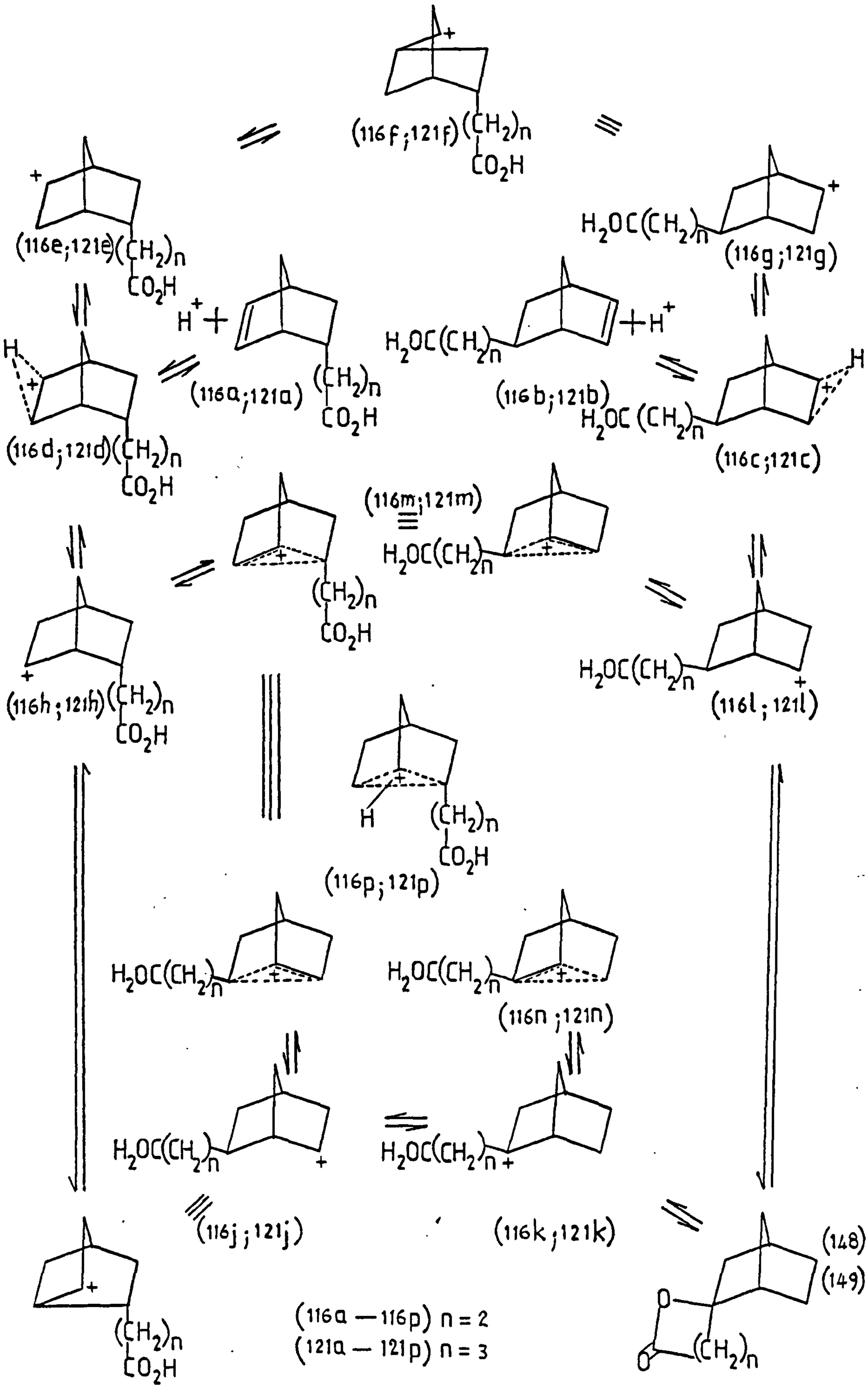
It has been proposed[93,132] that the positions of >C= O shifts in cyclic ketones and lactones can be correlated with ring size. The ^{13}C resonance is at lower field in five membered than in six membered rings. This is consistent with the data for the lactones (148) and (149). The >C= O shifts in the γ-lactone (148) at δ176.67 is at lower field than that

for the δ-lactone (149) at δ171.4. These shifts are consistent with those earlier reported[93] for the >C = O shifts of the iodoγ-lactones (122), (135) and the iodoδ-lactone (132) at δ178.3, 176.0 and 168.0 respectively.

2.3.1.5. The mechanism involved in the formation of lactones (145a; b),[94] (146a; b),[132] (147a; b)[94] and (147c; d)[128] is well documented. Scheme 13 indicates the proposed mechanism as to how both <u>endo</u> and <u>exo</u> acids (116a; b) and <u>endo</u> and <u>exo</u> acids (121a; b) afforded the spiroδ-lactone (149) and the spiroγ-lactone (148) respectively. The 'onium ion intermediates (116c; 121c) and (116d; 121d) preferentially collapse to classical carbocations (116h; 121 h) and (116l; 121l) respectively which in terms of non-classical carbocation means (116m; 121m). The classical carbocations (116h; 121h) may be considered to undergo Wagner-Meerwein rearrangement to give carbocations (116j; 121j).
A 6-<u>endo</u>,2-<u>endo</u> hydride shift cannot occur because of the <u>endo</u>-carboxylic acid function at C-2. The favourable nature of 5,6-<u>exo</u>, <u>exo</u>, 3,2-<u>endo</u>, <u>endo</u> and 2,6-<u>endo</u>, <u>endo</u> hydride shifts in norbornane systems are well documented.[64,82b]
Both of the classical carbocations (116j; 121j) and (116l; 121l) can undergo 2,6-<u>endo</u>, <u>endo</u> hydride shifts leading to the classical carbocations (116k; 121k). Intramolecular cyclisation by the carboxyl group to the tertiary carbocation centre in (116k; 121k) may afford the lactones (148) and (149) respectively. The <u>exo</u>-cyclisation of the carboxyl group is based on the high known preference for <u>exo</u>-attack on a tertiary norbornyl cation.[64,82b,77b]

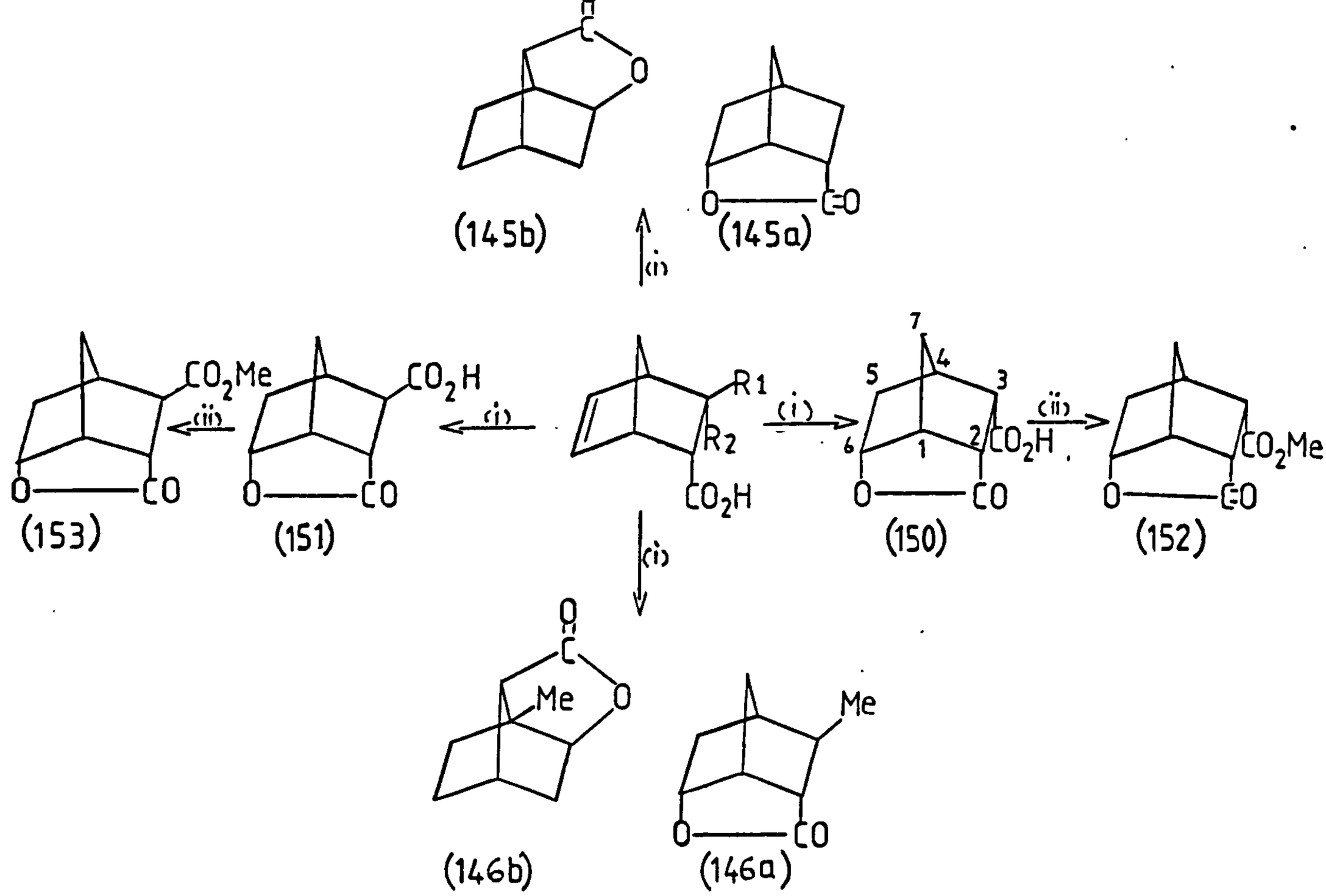
Instead of the classical carbocations (116e; 121e) - (116l; 121l) the formation of lactones (148) and (149) also may be considered <u>via</u> the non-classical carbocations (116m; 121m) - (116n; 121n), for which (116p; 121p) is a composite.

Scheme 13


(116e;121e)
(116f;121f)
(116g;121g)
(116a;121a)
(116b;121b)
(116c;121c)
(116d;121d)
(116m;121m)
(116h;121h)
(116l;121l)
(116p;121p)
(116n;121n)
(116j;121j)
(116k;121k)
(148) n = 2
(149) n = 3
(116a — 116p) n = 2
(121a — 121p) n = 3

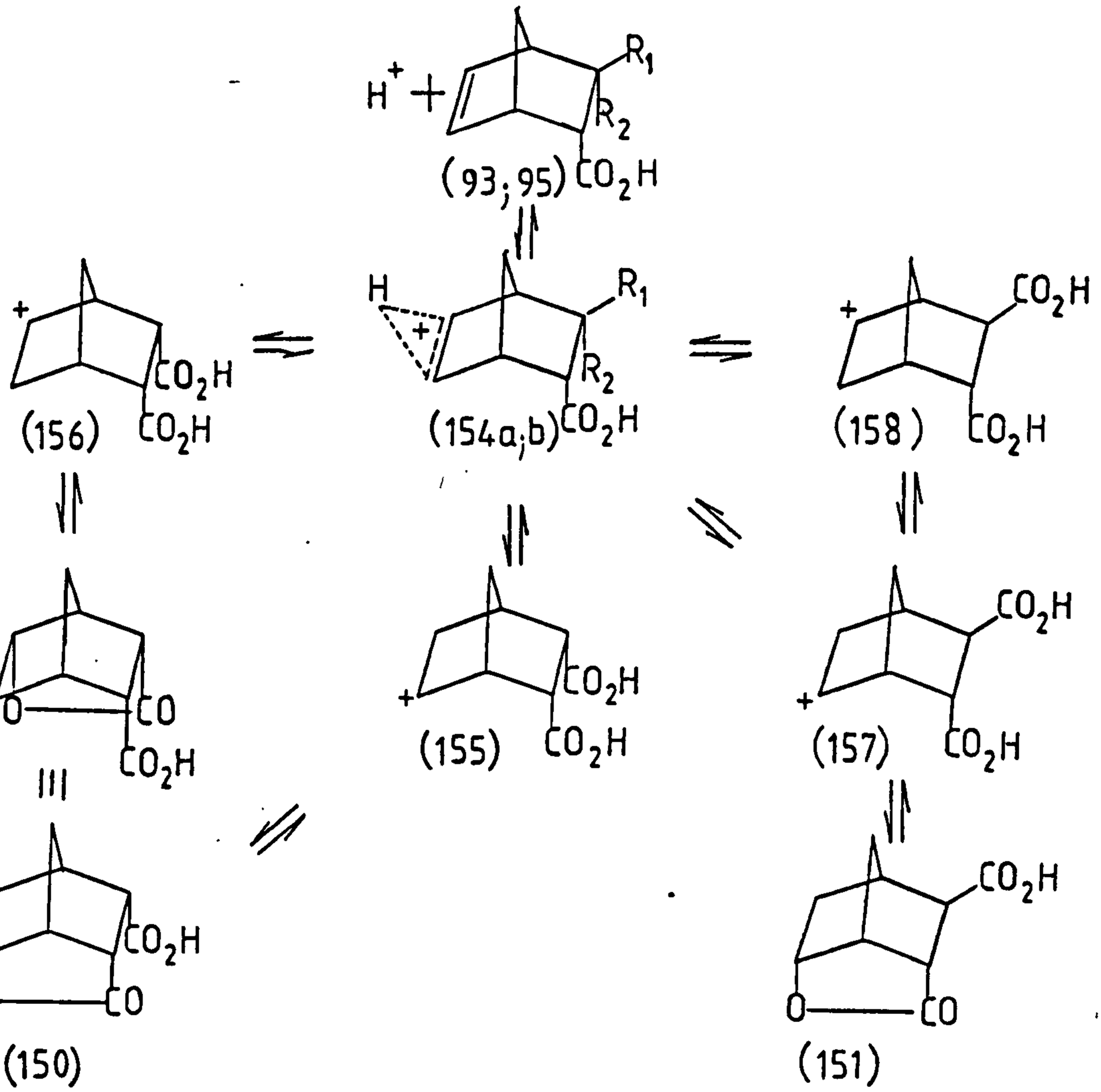
2.3.1.6. Acid catalysed lactonisation of norborn-5-en-2-endo, 3-endo-yldicarboxylic acid (93) and norborn-5-en-2-endo, 3-exo-yldicarboxylic acid (95).

Scheme 14



The unsubstituted endo-acid (91a) and 3-exo-methylnorborn-5-en-2-endo-ylcarboxylic acid (96a)[methyl is an electron donating group] were reported earlier to afford mixtures of the lactones (145a; b) and (146a; b) respectively on treatment with sulphuric acid. The acids (93) and (95) which have an electron withdrawing carboxyl group at the C-3 position afforded only the unrearranged product lactones (150) and (151) in yields of 55% and 64% respectively on treatment with sulphuric acid. Both of the lactones (150) and (151) exhibited in the infrared a broad medium absorption at 3380-2500 cm^{-1} (-COOH) and two strong absorptions at 1760 cm^{-1} (>C=O of a γ-lactone) and 1710 cm^{-1} (>C= O of acid). The structures (150) and (151) were further established by the ^1H nmr which showed a s at δ8.1 (-COOH), a brt at δ4.73 (150) and δ4.90 (151) for (>CH-O) with J(6-exo, 1) = J(6-exo, 5-exo) = 6 Hz, a brt at δ3.20 (150; 151) of H-1 with J(1,6-exo) = J(1,2-exo) = 6 Hz, a t at δ2.75 (150) and a brd at δ2.90 (151) for H-4 with J(4,5-exo) = 5 Hz. On methylation of the acids (150) and (152) with diazomethane the ester γ-lactones (152) and (153) were obtained in yields of 88% and 97% respectively. The esters (152) and (153) had strong absorptions at 1760 cm^{-1} (>C= O of a γ-lactone) and at 1735 cm^{-1} (>C= O of an ester). The ^1H nmr of (152) and (153) contained a brt at δ4.80 (152; 153) for >CH-O with J(1,6-exo) = J(5-exo, 6-exo) = 6 Hz, a s at δ3.70 (152) and δ3.73 (153) for $-OCH_3$.

Scheme 15



Scheme 15 shows the most likely mechanism for the formation of the lactones (150) and (151). The exo-protonation of (93) and (95) gives the 'onium ion intermediate (154a; b). The 'onium ion (154a) R_1 = H, R_2 = COOH collapses to the classical carbocations (155) or (156) both of which lead on cyclisation to the same lactone (150) as the sole product. The 'onium ion (154b) R_1 = COOH, R_2 = H collapses preferentially to the classical carbocation (157) prior to cyclisation to afford the lactone (151); if the carbocation (158) was produced, it would undergo 5,6-endo, endo hydride

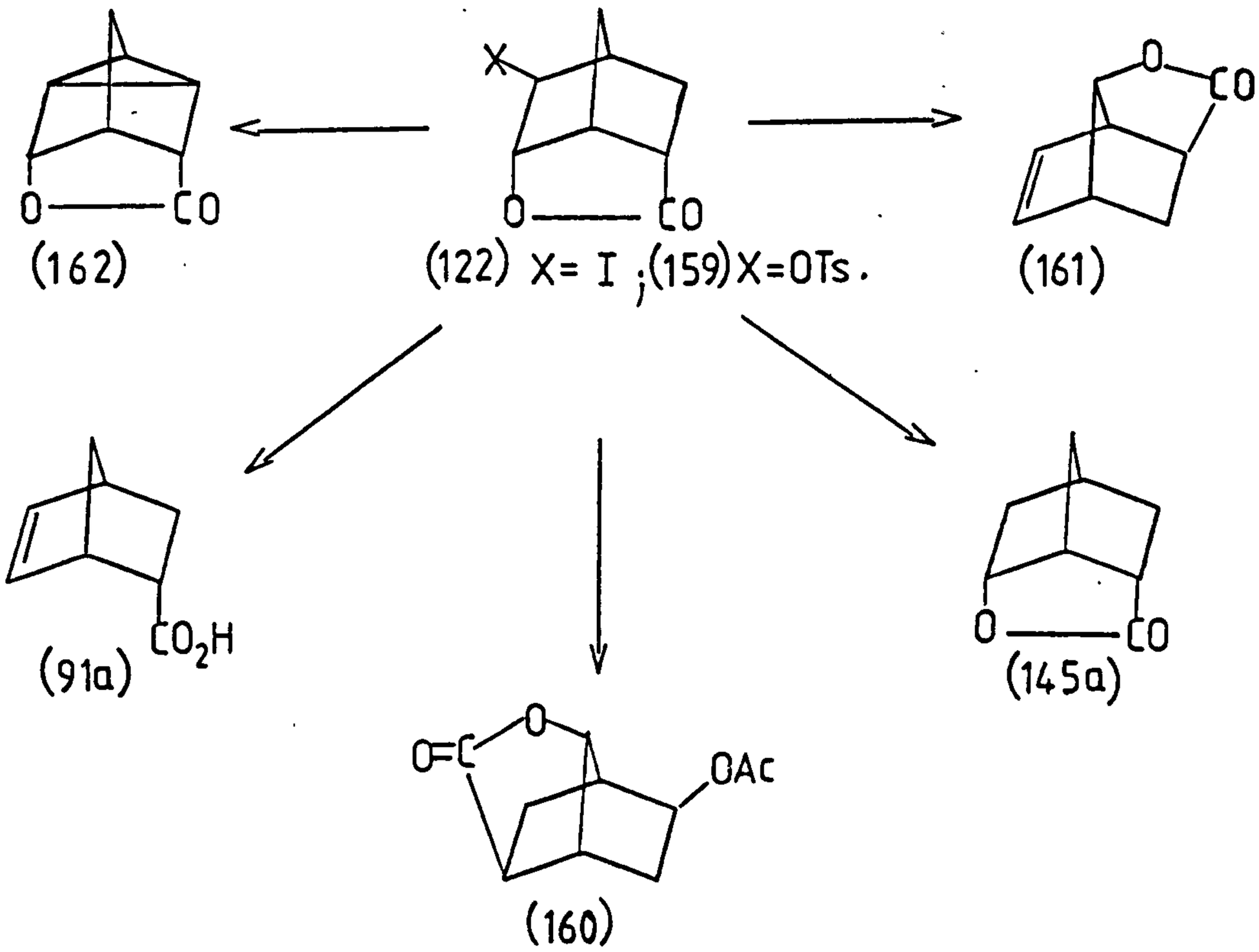
shift to (157) prior to formation of the product lactone (151). The formation of the lactones (150) and (151) can also be considered *via* intramolecular cyclisation of carboxylic acid function to the 'onium ion (154a; b) without collapse to classical carbocation (155) and (157) respectively. The absence of rearrangement products such as are found for the acids (91a) and (96a) indicates that the presence of carboxylic acid function at C-3 in (93) and (95) inhibits 3,5-*endo*, *endo* hydride shifts in (156) and (158) and makes the electrons in the C-3 - C-4 bond less available for a Wagner-Meerwein rearrangement.

TABLE 14. ^{1}H nmr data of the lactones (146a and 150-153).

Compound	δ (ppm)								
	1	2-*exo*	3-*exo*	3-*endo*	4	5-*exo*	6-*exo*	7-*syn*	7-*anti*
146a	t 3.10	m 2.10	d 1.10	m 1.25	m 2.10	m 2.10	t 4.75	m 1.80	
150	t 3.20	m 2.70		s 8.2	brt 2.75	m 1.80	t 4.80	m 1.78	
151	m 3.18	m 2.80	s 8.2	m 2.70	brd 2.90	m 1.70	t 4.90	m 1.80	
152	m 3.25	m 2.70	s 3.70	m 2.92	m 2.0	t 4.80	m 1.80		
153	m 3.20	m 2.75	s 3.73	m 2.70	m 3.20	m 1.70	t 4.80	m 1.70	

2.4.0.0. Reaction of silver tosylate with the iodolactones derived from norborn-5-en-2-endo-ylcarboxylic acid derivatives.

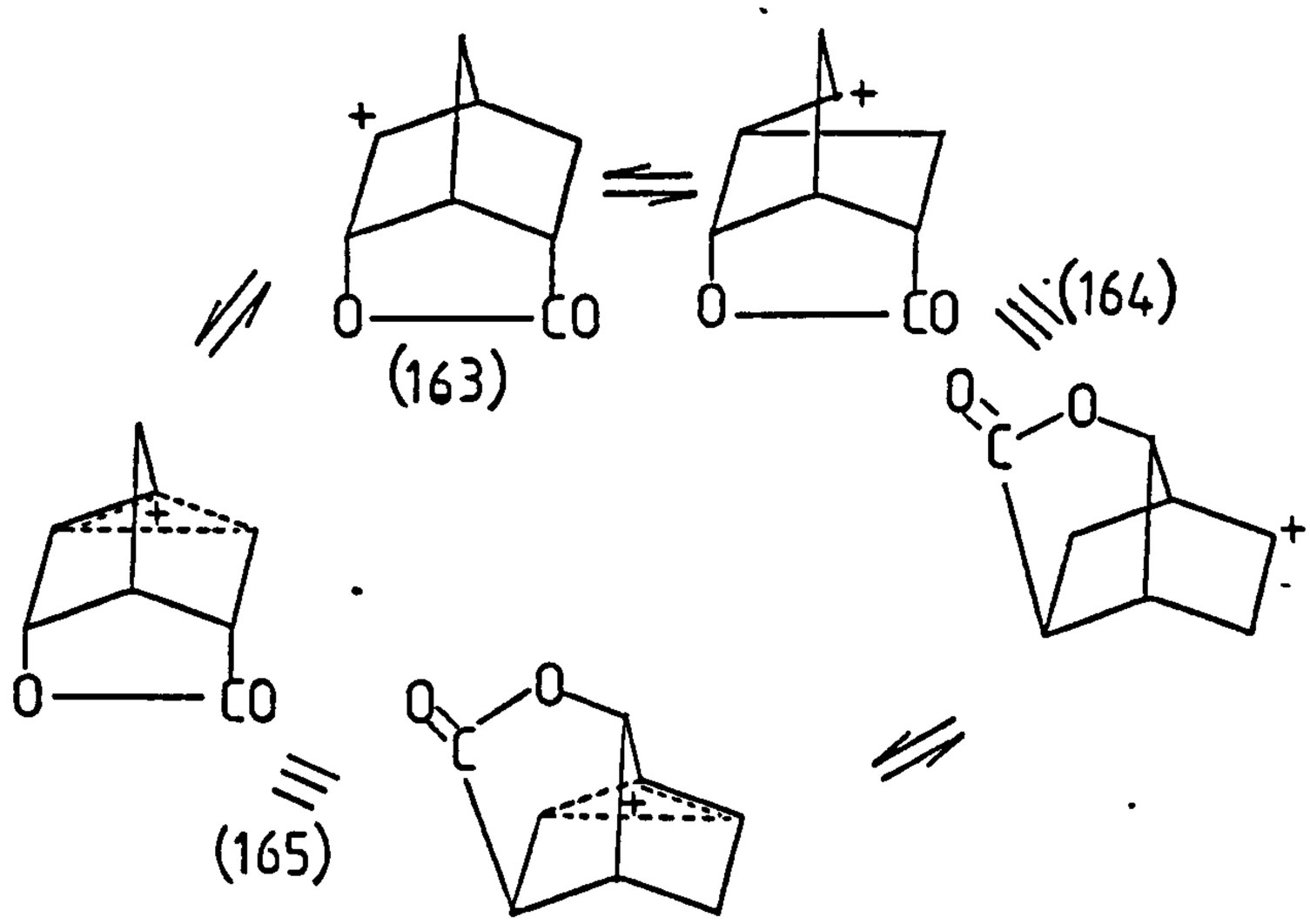
2.4.1.1. Introduction.



Moriarty et al.[133] as part of his study of neighbouring group dipolar effects upon solvolytic reactivity observed that the acetolysis of 5-exo-tosyloxy-6-endo-hydroxynorborn-2-endo-ylcarboxylic acid γ-lactone (159) afforded 3-exo-acetoxy-7-syn-hydroxynorborn-6-exo-ylcarboxylic acid γ-lactone (160) as the sole product. Later Kropp[134] reported that when the iodoγ-łactone (122) was subjected to photolysis at 253.7 nm in a quartz vessel in ether solution, a mixture of the lactones (145a), (161), (162) and the acid

(91a) were obtained in relative yields of 36%, 18%, 18% and 24% respectively.

The formation of the acetoxy lactone (160) was proposed[133] as occurring *via* carbocation (163); in order to diminish the dipolar destabilisation (effects of lactone dipole) the carbocation (163) was thought to undergo Wagner Meerwein rearrangement to (164), in which the positive centre is further remote with respect to the positive end of the lactone dipole, and is captured by the acetate ion to give the product (160).



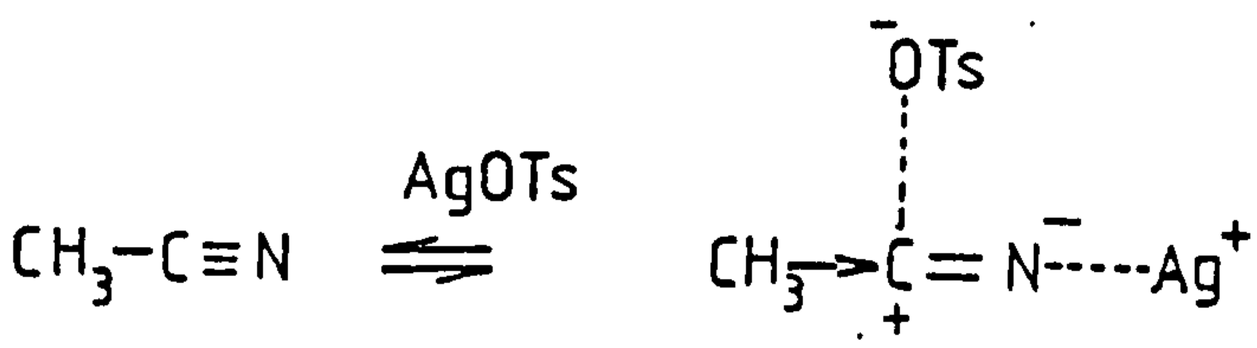
The involvement of cationic intermediates in the product formation of the unsaturated lactone (161) and the notricyclene lactone (162) was considered by Kropp[134] in the photolysis of iodoγ-lactone (122). The non-classical ion (165) which is a composite of the classical ions (163) and (164) would undergo elimination to afford the product lactones (161) and (162). This led Kropp to propose that the photochemical behaviour of alkyl iodides and

iodolactones in solution was greatly varied and did not lead invariably to only free radical-type products; the lactone (145a) in case of the iodoγ-lactone (122).

Because of the possible ambiguity in the photochemistry of alkyl iodides as a means of producing carbocations, it was desirable to seek an alternative method of producing such intermediates from the iodolactone derived from norborn-5-en-2-endo-ylcarboxylic acid derivatives.

The method chosen was that of Hoffmann,[50] who showed that an alkyl iodide, when treated with silver tosylate in acetonitrile solution, affords an alkyl tosylate via an intermediate carbocation. Silver tosylate is easily prepared[50] by reaction of an aqueous solution of silver nitrate with an aqueous solution of sodium toluene-p-sulphonate at 5°; the product silver tosylate is precipitated as a white-grey shining solid.

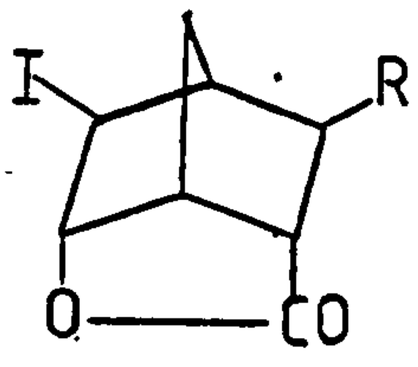
The higher solubility of silver tosylate in acetonitrile, which led to it being the chosen solvent is due to its ability to form a high degree of solvation with silver cations. The stronger cationic solvation compared to the anionic solvation results in increased reactivity of tosylate anion towards nucleophilic displacement of iodide anion.



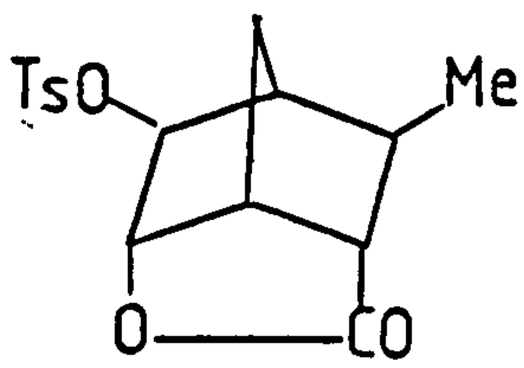
The weaker anionic solvation is caused by the electron donating methyl group, which further stabilises the positive carbon..

2.4.1.2. Reaction of 6-endo-hydroxy-5-exo-iodonorborn-2-endo-ylcarboxylic acid γ-lactone (122) and 6-endo-hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylcarboxylic acid γ-lactone (127) with silver tosylate.

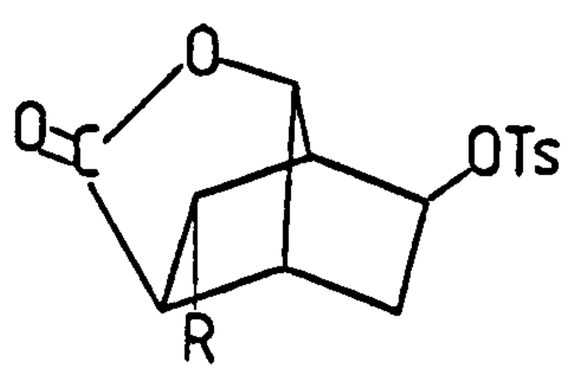
Scheme 17



(122) R = H; (127) R = Me.



(168)



(166) R = H; (167) R = Me.

Addition of a solution of iodoγ-lactone (122) to a solution of silver tosylate in acetonitrile proceeded under protection from light at 5°; the mixture was left to warm up to room temperature for a further 1 h and then heated at reflux for 8 h, as a yellow precipitate of silver iodide gradually formed. Dilution of the filtrate with water followed by extraction with dichloromethane and removal of the solvent afforded a mixture of product (166) contaminated with the starting iodoγ-lactone (122). Separation by p.l.c. with chloroform as eluent afforded 7-syn-hydroxy-3-exo-tosyloxynorborn-6-exo-ylcarboxylic acid γ-lactone (166), R_F 0.44 in a yield of (55%).

The same treatment of the iodoγ-lactone (127) with silver tosylate, apart from a longer time at reflux (40 h) gave a mixture of products (168) and (167) contaminated with starting iodoγ-lactone (127). On separation by p.l.c. with 2:3 ethyl acetate/light petroleum b.p. 60-80° as eluent the products (167) R_F 0.43 and (168) R_F 0.52 were

obtained in a 1:7.5 molar ratio. The products (166), (167) and (168) exhibited strong absorptions at 1790, 1780 and 1790 cm^{-1} respectively (>C=O of a γ-lactone) in the infrared . The structure of (166) and (167) is further supported by the ^1H nmr with the help of spin-decoupling experiments (Table 15).

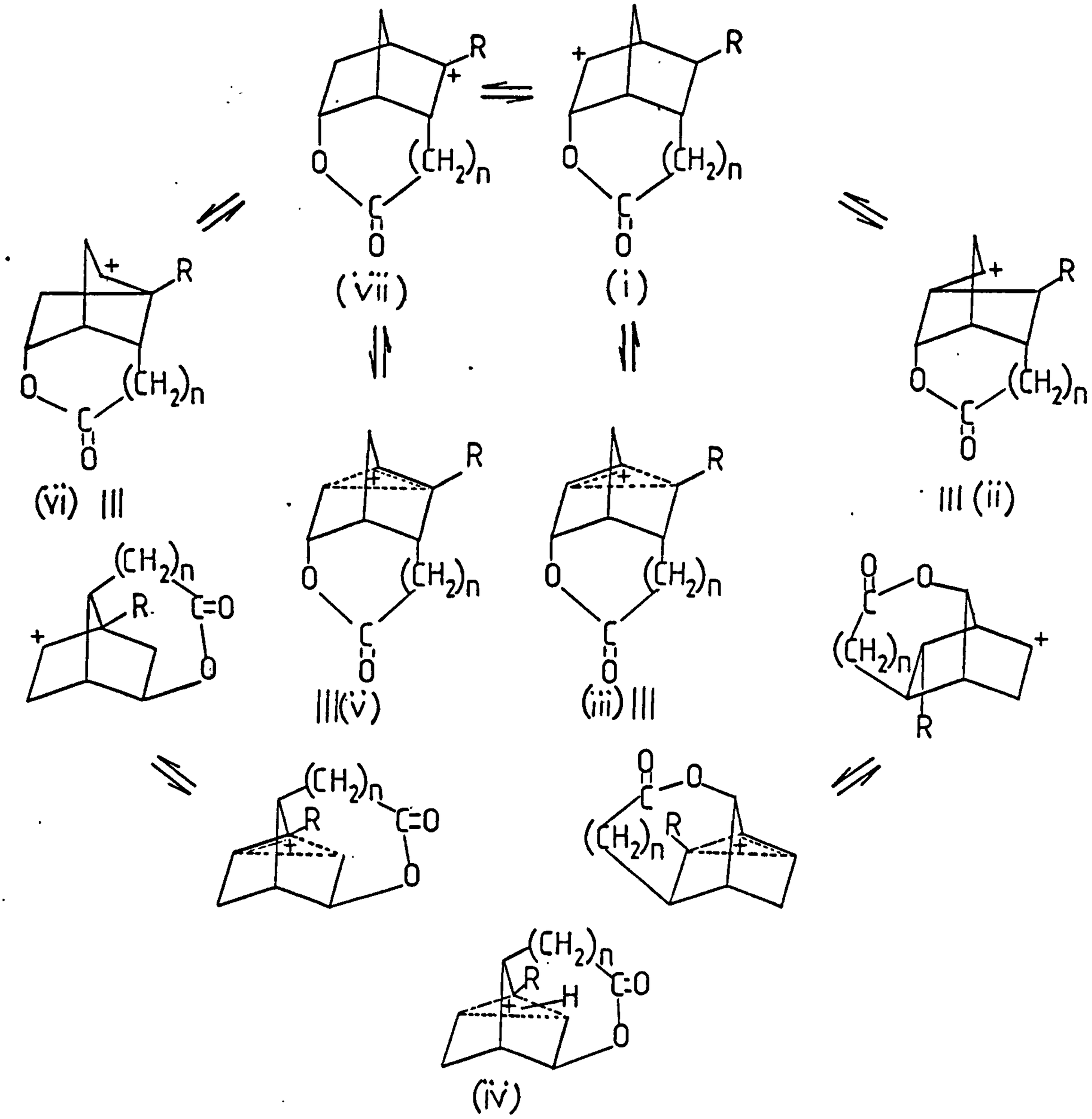
TABLE 15. Spin-decoupling experiments on compounds (167) and (166).

Compound	Irradiated protons	δ	Observation
166	H-1,H-4	2.90	Sharpening of brs at δ5.15 of H-7anti, brq at δ1.96 of 4-2-endo becomes a sharp q, J(2-endo,2-exo) 16 and J(2-endo,3-endo) 6 Hz, collapse of m at δ1.65 of H-2-exo to a q, J(2-endo, 2-exo)16 and J(2-exo,3-endo)2Hz.
	H-3endo	4.08	Collapse of q at δ1.96 of H-2endo to a d, J(2-endo, 2-exo)16Hz, together with a small change in m at δ1.65 of H-2exo .
	H-5exo	3.41	Changes at δ2.90 of H-4 and δ3.18 of H-6endo.
	H-7anti	5.15	Collapse of t at δ3.18 of H-6endo to a d, J(5-exo, 6-endo)2Hz, together with small changes at δ2.90 of H-1 and δ1.96 of H-2endo.
167	H-7anti	5.03	Collapse of a m at δ2.69 of H-6endo to a d, J(6-exo, 5-exo)5 Hz.
	H-3endo	4.85	Collapse of a q at δ2.03 of H-2endo to a d, J(2-endo, 2-exo)14 Hz, and of a m at δ2.23 of H-2exo to a q, J(2-exo, 2-endo) 14 Hz, J(2-exo, 1)6 Hz.

The structure of the tosyloxyγ-lactone (168) is easily recognised from the ^1H nmr spectrum which contained a d at δ7.75 of ortho-Aromatic, a d at δ7.35 of meta-Aromatic with J(ortho, meta) = 8 Hz, a d at δ4.45 of >CH-O with J(1,6-exo) = 6 Hz, a brs at δ4.22 of >CH-OTs,a brt at δ3.13

of H-1 with J(1,6-exo) = J(1,2-exo) = 6 Hz, and a d at δ1.09 of CH_3 with J(CH_3, H-3endo) = 8 Hz. The summary of the ^1H nmr data for compounds (166), (167), and (168) is given in Table 16.

Scheme 18



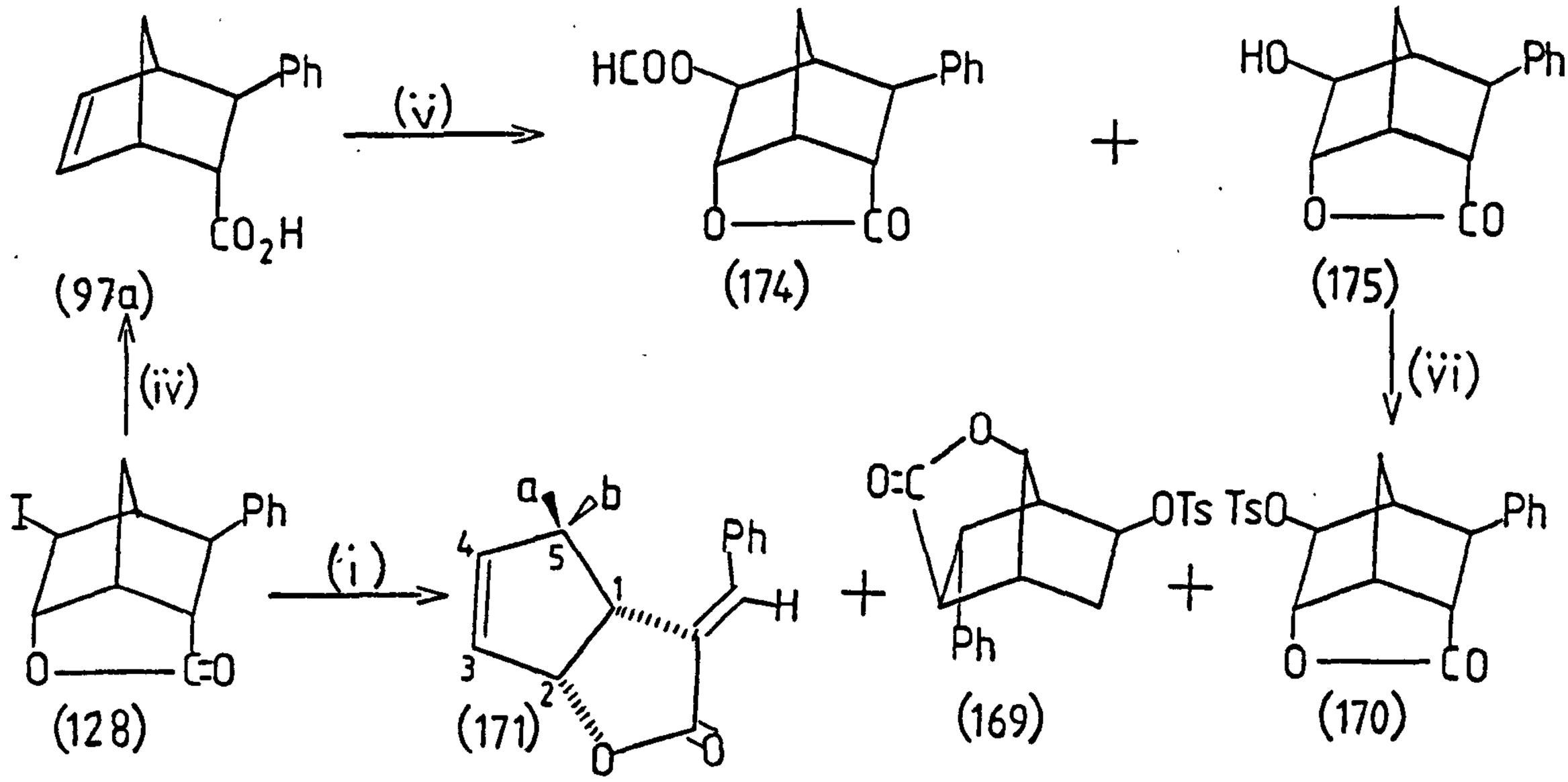
Scheme 18 shows diagrammatically the mechanism involved in product formation. Ionisation of (122) gave the classical carbocation (i; R = H, n = 0) which would undergo Wagner-Meerwein rearrangement to classical carbocation (ii; R = H, n = 0). The cation (ii; R = H, n = 0) is more stable compared with the cation (i; R = H, n = 0), because the carbocation centre is remote from the electron withdrawing carbonyl group, and is captured by the tosylate ion to afford the tosyloxyγ-lactone (166). The classical cation (i; R = CH_3, n = 0) results from ionisation of the iodoγ-lactone (127) and because of the presence of methyl (electron donating group) is possibly stabilised and less likely to equilibrate with the carbocation (ii; R = CH_3, n = 0). This assumption is based on the relatively higher yields of (168) than (167) isolated in 7.5:1 molar ratio. Instead the classical carbocations (i) - (ii) R = CH_3, H, n = 0; the non-classical ion (iii; R = CH_3, H; n = 0) can also be considered in the formation of the tosyloxyγ-lactones (166) - (168).

TABLE 16. ^{1}H nmr data of (166) - (168).

Compound	δ (ppm)													
	1	2-exo	2-endo	3-exo	3-endo	4	5-exo	5-endo	6-exo	6-endo	7-anti	7-syn	ortho	meta	p-CH_3
166	m 2.66	m 1.80			brq 4.69	m 2.66	m 1.80	brq 1.33		m 2.66	brs 4.99		d 7.79	d 7.36	s 2.46
167	brd 2.54	m 2.23	q 2.03		brq 4.85	m 2.28	brd 1.90	d 1.07		m 2.69	brs 5.03		d 7.75	d 7.35	s 2.46
168	brt 3.13	brd 2.06		d 1.09	m 1.78	brs 2.13		brs 4.22	brd 4.45		m 1.89		d 7.75	d 7.35	s 2.46

2.4.1.3. Reaction of 6-endo-hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo-ylcarboxylic acid γ-lactone (128) with silver tosylate.

Scheme 19



(i) AgOTs — MeCN. (ii) $LiAlH_4$ — Et_2O. (iii) PDC — DMF.

(iv) Zn — AcOH. (v) H_2O_2 — HCO_2H. (vi) TsCl — Py.

Treatment of the iodoγ-lactone (128) with silver tosylate and then heating at reflux for 48 h provided an unexpected result. The crude product, obtained on working up the reaction mixture showed when spotted on a t.l.c. plate and eluted with ethyl acetate-light petroluem b.p. 60-80° (3:7) 3 major spots at R_F0.43, 0.35 and 0.25 respectively none of which corresponded to the starting iodoγ-lactone (128) R_F0.6. By separation on p.l.c. it was possible to isolate, in addition to the tosyloxyγ-lactones (170) R_F0.35 and (169) R_F0.25 anticipated on the basis of the results with iodoγ-lactone (127), the unsaturated γ-lactone (171). These products (169), (170) and (171) were obtained in a 1:2.2:7.8 molar ratio, and their ir spectrum showed a strong absorption at 1790, 1800, and 1760 cm^{-1} (>C= O of a γ-lactone) respectively. The ^1H nmr spectrum of the tosyloxyγ-lactone (169) showed a d at δ7.62 (ortho-Aromatic), a d at δ7.12 (meta-Aromatic) with J(ortho, meta) = 8 Hz, a brs at δ5.15 (H-7anti), a d at δ4.08 (H-3-endo) with J(3-endo, 2-endo) = 6 Hz, a d at δ3.41 (H-5exo) with J(5-exo, 4) = 6 Hz and overlapping m at δ3.18-1.65 containing a sharp s at δ2.42 of p-CH_3. The structure (169) is further supported by the spin-decoupling experiments reported in Table 18. The second major product was the tosyloxyγ-lactone (170) which was easily identified since the ^1H nmr spectrum showed doublets at δ7.83 (ortho-Aromatic) and δ7.35 (meta-Aromatic) with J(ortho, meta) = 8 Hz, a m at δ7.19 (Ph), a d at δ4.56 (>CH-O-) with J(1,6-exo) = 3 Hz, a brs at δ4.40 (H-1), and overlapping m at δ3.15-1.99 containing a sharp s at δ2.46 (p-CH_3). In an attempt to further confirm the structure

for (170), it was prepared by an alternative route. Reduction of the iodoγ-lactone (128) with zinc in acetic acid[129] afforded 3-exo-phenylnorborn-5-en-2-endo-ylcarboxylic acid (97a) in a yield of 74%. The acid (97a) showed a medium broad absorption 2500-3300 cm^{-1} (-COOH) and a strong absorption at 1710 cm^{-1} (>C=O of acid). The ^1H nmr contained a s at δ10.3 (OH of acid), a m at δ3.35 (H-1, H-4, H-2exo) and overlapping m at δ3.0-1.7 of (H-3endo, H-7syn, H-7anti). Oxidation of the acid (97a) by reaction with hydrogen peroxide and formic acid at 45-50° for 1 h, gave a mixture of the hydroxyγ-lactone (175) and the formyloxyγ-lactone (174). These products (174) and (175) on separation and purification by p.l.c., with chloroform as the eluent, were isolated in 1:4·2 molar ratio. The product (174) exhibited strong absorptions at 1785 (>C=O of a γ-lactone) and 1730 cm^{-1} (>C=O of an ester). The structure of (174) is supported by the ^1H nmr which showed a s at δ8.05 (HCOO-), a m at δ7.25 (Ph), a brs at δ4.85 (>CHO-), a d at δ4.60 (>CH-O-) with J(1,6-exo) = 5 Hz, a m at δ3.20 (H-1, H-4) and an overlapping m at δ2.80-1.95 of high field protons. The hydroxyγ-lactone (175) exhibited in the infrared a medium absorption at 3480 cm^{-1} (OH) and a strong absorption at 1780 cm^{-1} (>C=O of a γ-lactone). The ^1H nmr of (175) showed a m at δ7.25 (Ph), a brd at δ4.45 (>CH-O-), a brs at δ3.85 (>CHO-), a brs at δ3.70 (OH), and overlapping resonance at δ3.10-1.92.

Treatment of the hydroxyγ-lactone (175) with tosyl chloride in pyridine for 40 h in the refrigerator gave

the required 6-endo-hydroxy-3-exo-phenyl-5-exo-tosyloxynorborn-2-endo-ylcarboxylic acid γ-lactone (170) in 74% yield. The ^1H nmr and ir spectroscopic data and the physical properties were identical with those of tosyloxyγ-lactone (170) previously obtained from the reaction of silver tosylate with the iodoγ-lactone (128).

TABLE 18. Spin-decoupling experiments on compounds (169), (171) - (173).

Compound	Irradiated protons	δ	Observations
169	H-1,H-4	2.90	Sharpening of brs at δ5.15 of H-7anti, brq at δ1.96 of H-2endo becomes a sharp q, J(2-endo, 2-exo)16 and J92-endo, 3-endo) 6Hz collapse of m at δ1.65 of H-2exo to a q, J(2-endo, 2-exo)16 and J92-exo, 3-endo)2Hz.
	H-3endo	4.08	Collapse of q at δ1.96 of H-2endo to a d, J(2-endo, 2-exo)16 Hz, together with a small change in m at δ1.65 of H-2exo.
	H-5exo	3.41	Changes at δ2.90 (H-4) and δ3.18 (H-6endo).
	H-7anti	5.15	Collapse of t at δ3.18 of H-6endo to a d, J(5-exo,6-endo)2 Hz, together with small changes at δ2.90 (H-1) and δ1.96 (H-2endo).
171	H-2	5.60	Collapse of m at δ4.07 of H-1, qxm at δ3.11 of H-5a, and dxm at δ2.43 of H-5b.
	H-5a	3.11	Collapse of dxm at δ2.43 of H-5b to two overlapping d, J(5b,1)4 and J(5b,H)2 Hz.
	H-5b	2.43	Collapse of qxm at δ3.11 of H-5a and of m at δ4.07 of H-1, and a small change at δ5.94 of H-4.
	H-8 and Ph	7.50	Sharpening of m at δ4.07 of H-1 to 2q, J(2,1)9, J(5a,1)9.5, and J(5b,1)4 Hz.

... Continued ...

TABLE 18 (continued)

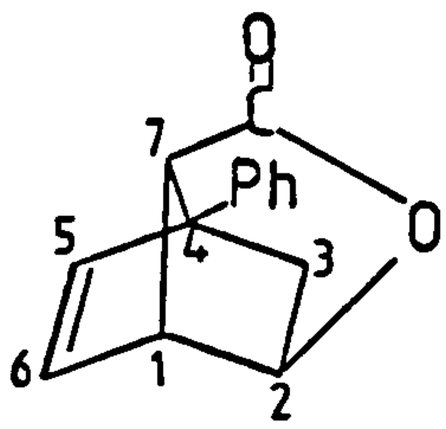
Compound	Irradiated protons	δ	Observations
	H-1	4.07	Collapse of dxm at δ5.60 of H-2 to brs, collapse of qxm at δ3.11 of H-5a to d, J(5a, 5b)17 Hz, and sharpening of brs at δ7.48 of H-8.
172	H-2	4.60	Collapse of m at δ3.46 of H-1, dxm at δ2.41 of H-5a, and a dxm at δ2.26 of H-5b.
	H-5a and H-5b	2.35	Collapse of m at δ3.46 of H-1 to brd, J(2,1)7.5 Hz, and sharpening of brd at δ4.60 of H-2.
	Ph	7.19	Small changes at δ3.40 of H-1.
	H-3 and H-4	5.70	Small changes at δ3.46 of H-1, δ2.26 of H-5b and δ2.41 of H-5a.
	H-1	3.46	Collapse of brd at δ4.60 of H-2 to brs and changes at δ2.41 of H-5a and at δ2.26 of H-5b.
173	H-5a, H-5b	2.86	Collapse of brt at δ3.65 of H-1 to brs, dxt at δ6.31 of H-4 to d, J(4,3)6 Hz, and q at δ7.74 of H-3 to d, J(4,3)6 Hz.
	H-4	6.31	Collapse of q at δ7.74 of H-3 to d, and changes at δ2.86 of H-5a and H-5b.
	H-1	3.65	Collapse of m at δ2.86 of H-5a and H-5b to a q, and of d at δ9.49 of H-6 to s.

The unsaturated γ-lactone (171) is the major product obtained from the reaction of silver tosylate with the iodo$_\gamma$-lactone (128). The ^{1}H nmr spectrum of (171) is difficult to interpret and initially we reported[136] that the structure was that of the unsaturated γ-lactone (176) and not (171). In the aromatic region a multiplet was observed centred at δ7.50 integrating for six protons. That the additional non-aromatic proton in this region was

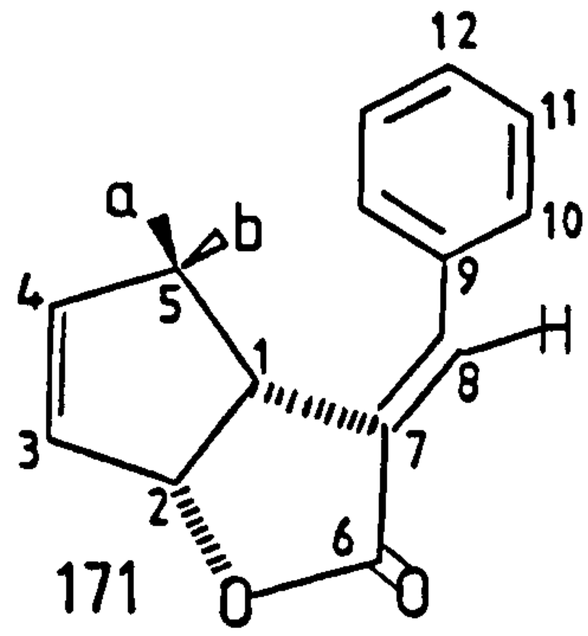
not an olefinic proton shifted to lower field was clear since the olefinic protons at C-5 and C-6 (176) were present as a multiplet at δ5.99 integrating for two protons. We thought the exceptionally low field proton was that at the bridge head C-1 position. Bridge head protons at C-1 are known from nmr spectral studies of norbornenes[87] to usually occur in the region δ3.5-2.5. The remarkable downfield shift to δ7.50 was suggested as being due to the deshielding of H-1 on account of the anisotropy of the double bond, the aromatic ring, and the ester carbonyl group, as well as the inductive effect of ester oxygen. The correct structure of α-(cis-2-hydroxycyclopent-3-en-1-yl)-E-cinnamic acidγ-lactone (171) was based on further spectral evidence. The ir spectrum exhibited a strong absorption at 1760 cm^{-1} (>C=O of a γ-lactone) shifted to lower frequency compared to carbonyl absorptions at 1790 and 1800 cm^{-1} in (169) and (170) respectively. This is due to the conjugation of the carbonyl group with the double bond consistent with the structure (171).

In the ^{1}H nmr, the non-aromatic proton at δ7.50 may also be assigned to H-8, a site appropriate for an olefinic proton in a cinnamic acid derivative.

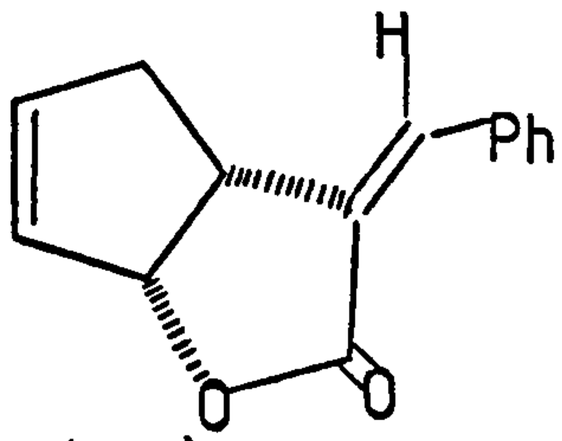
Scheme 19A



(176)



171



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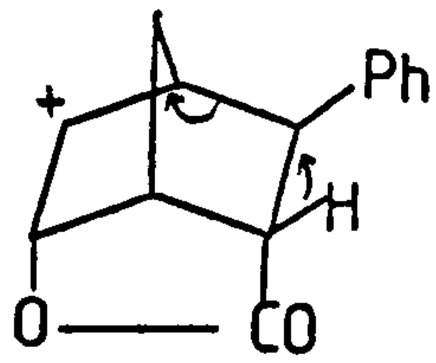
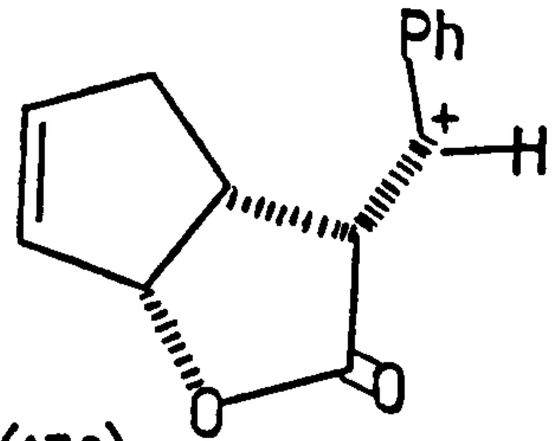
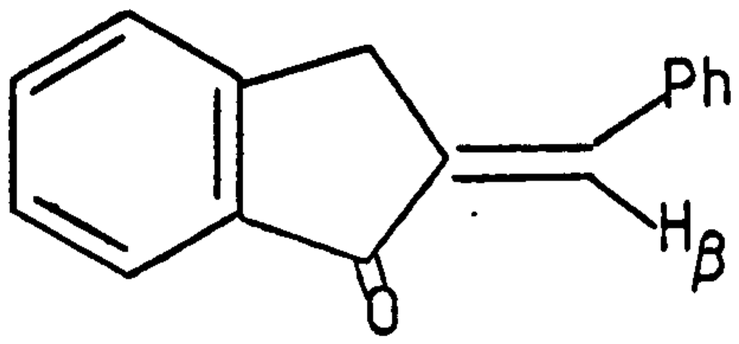


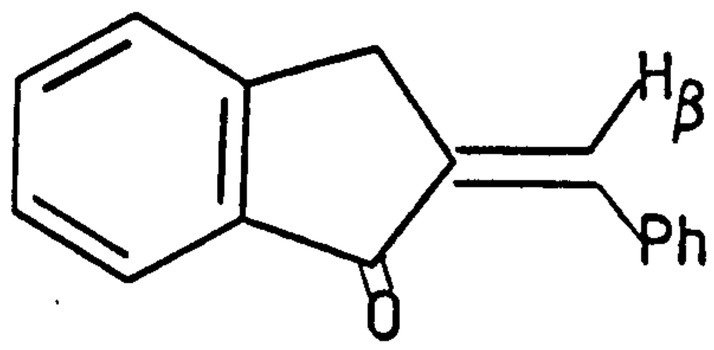
(178)



(179)



(180) H-β at δ 7·45 .



(181) H-β at δ 6·88 .

Comparison with the published ^{1}H nmr data on 2-benzalindan-1-ones (180) and (181)[137] indicate that the position of H-8 is consistent only with the E-isomer (171), and not the Z-isomer (177) for which H-8 would be expected to be at about δ6.80 as in (191). With the help of spin-decoupling experiments given in Table 18, the summary of the ^{1}H nmr data is reported in Table 19. The ^{13}C nmr data given in Table 20 additionally supports the structure (171) and clearly indicates the presence of

three saturated and eleven unsaturated carbon atoms. The three saturated carbon atoms which have no proton attached, give rise to resonances as singlets at δ172.2, 133.9 and 129.5 and correspond to C-6, C-9 and C-7 respectively. The ultraviolent spectrum for (171) in methanol showed λ max 284 nm (ε21,284). The ethyl esters of Z- and E-cinnamic acid are reported[138] to exhibit U.V. λ max in ethanol solution at 266 nm (ε9772) and 275 nm (ε19,950) respectively. If Woodward's generalisations[139] for α,β-unsaturated carbonyl systems can be applied to cinnamic acid derivatives, then the calculated λ max for (171) should be 285 nm i.e. that for ethyl E-cinnamate plus 5 nm each for an α-substituent and the exocyclic nature of the double bond. For (177) the calculated value is 276 nm so that the observed value is consistent only with the structure (171). Reduction of the unsaturated γ-lactone (171) with lithium aluminium hydride afforded the unsaturated diol (172) in 80% yield. In the ir spectra, the diol (172) exhibited a medium absorption at 3380 cm^{-1} (OH) and the ^1H nmr clearly showed the deshielding effect due to the anisotropy at a lactone carbonyl group (in 171) because the proton H-8 is shifted to higher field as a s at δ6.60. A m at δ5.70 (olefinic protons) a brd at δ4.60 (>C<u>H</u>O-) with J(2,1) = 7.5 Hz, a brs at δ4.33 (O<u>H</u>) and a dxd at δ4.10 (>C<u>H_2</u>-O-) with J(6a,6b) = 12.5 Hz further support the diol structure (172).

Oxidation of the diol (172) with pyridiniumdichromate (PDC)[140] in anhydrous DMF at room temperature for 5 h gave the keto-aldehyde (173) in 73% yield. The ir

spectrum shows strong absorptions at 1710 and 1690 cm^{-1} for (>C = O of ketone) and (>C = O of aldehyde) respectively. The absorptions are consistent with conjugated carbonyl systems i.e. in comparison the carbonyl absorption of cyclopent-2-one[141] (185) occurs at 1710 cm^{-1}. The aldehyde proton of H-6 in (173) exhibits a d at δ9.50 with J(1,6) = 1 Hz. A q at δ7.74 (H-3) is shifted further downfield than the olefinic proton H-4 (dxt) at δ6.31 because of the deshielding effect due to the anisotropy of the carbonyl function at C-2. The anisotropy of the carbonyl of the aldehyde group at C-6 causes the proton at H-8 to be shifted downfield to δ7.65 consistent with the situation in (171). The chemical shift of the protons in (172) and (173) were assigned with the help of spin-decoupling experiments given in Table 18, and are reported in Table 20. The ultraviolent spectra of diol (172) and ketoaldehyde (173) showed λ max at 245 nm (ε6790) and 280 nm (ε18923) respectively. Because in (172) and (173) rotation could occur about the 1,7 and 6,7 bonds, leading to some departure from coplanarity in the conjugated system to minimise steric interference and electrostatic repulsion, the data for (172) and (173) although broadly consistent with the structures cannot be used as evidence for the geometry of the 7,8 double bond.

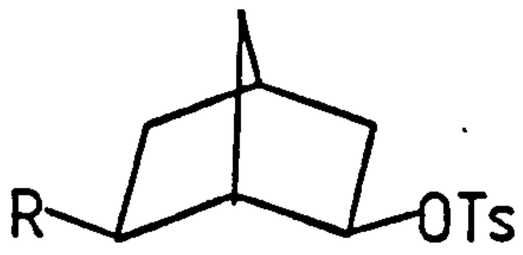
The most satisfactory explanation of these results involves the equilibrating classical carbocations (i; R = Ph, n = O) and (ii; R = Ph, n = O) as given in Scheme 18. Ionisation of the iodoγ-lactone (128) gave the

classical carbocation (i; R = Ph, n = O) which might be captured by the tosylate ion to afford the product (170). Alternatively (i; R = Ph, n = O) would undergo a Wagner-Meerwein rearrangement to give carbocation (ii; R = Ph, n = O), from which (169) is derived. However the formation of the major product of the unsaturated γ-lactone (171) required an alternative route. Our first report[136] was based on the incorrect structure (176) suggesting that the carbocation (i; R = Ph, n = O) was undergoing 3,5-endo, endo hydride shift[64,82b] to give the more stable benzyl-type norbornyl cation (vii; R = Ph, n = O). This was not captured by tosylate ion probably for steric reasons, and instead underwent a Wagner-Meerwein rearrangement to afford (vi; R = Ph, n = O), from which (176) might be derived by loss of a proton.

Finally the most probable mechanism which led to the observed product E-isomer (171) is the one stage fragmentation depicted in (178) as given in Scheme 19A. If there were to be a two stage process involving the benzylic cation (179) then the formation of (177) the geometrical isomer of (171) would also have been possible. Since (177) was not observed as a product, we favoured the reaction route depicted in (178). Grob[135] who also reported the involvement of one stage fragmentation in his studies on the solvolysis of 6-exo-substituted-2-exo-tosyloxynorbornanes (182) and (183) which gave a quantitative yield of cyclopent-3-en-1-ylacetaldehyde (184) consistent with the above proposals.

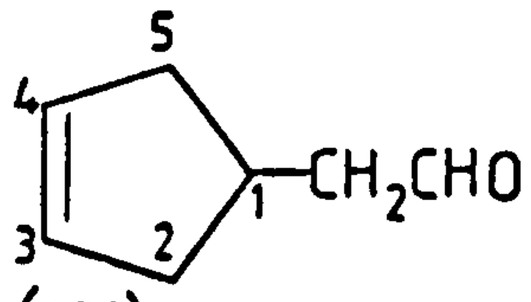
TABLE 19. ^{1}H nmr data for compounds (169) - (175).

Compounds	δ (ppm)													
	1	2-exo	2-endo	3-exo	3-endo	4	5-exo	5-endo	6-exo	6-endo	7-anti	7-syn	ortho	meta	p-CH_3
169	m 2.90	m 1.65	q 1.96		d 4.08	m 2.90	d 3.41	m 7.30	t 3.18		brs 5.15		d 7.62	d 7.12	s 2.42
170	m 3.15	brs 2.84		m 7.19	brm 2.84	m 3.15		brs 4.40	d 4.56		brm 1.99		d 7.83	d 7.35	s 2.47
174	m 3.20	m 2.80		m 7.25	m 2.80	m 3.20	s 8.05	brs 4.85	d 4.60		m 1.95				
175	m 3.10	m 2.80		m 7.25	m 2.80	m 3.10	brs 3.70	brs 3.85	brd 4.45		m 1.92				
	H-1	H-2	H-3	H-4	H-5a	H-5b	H-6	H-8	Ph	OH					
171	m 4.07	dxm 5.60	m 6.06	m 5.94	qxm 3.11	dxm 2.43		m 7.50							
172	m 3.46	brd 4.60	m 5.70		dxm 2.41	dxm 2.26	dxd 4.10	s 6.60	m 7.19	brs 4.33					
173	brt 3.65		q 7.74	dxt 6.31	m 2.86		d 9.50	s 7.65	m 7.43						

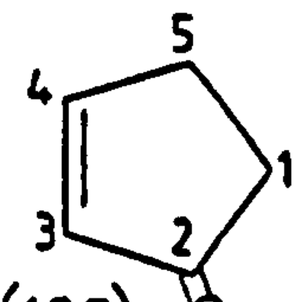


(182) R = NH_2

(183) R = $N(Me)_2$



(184)



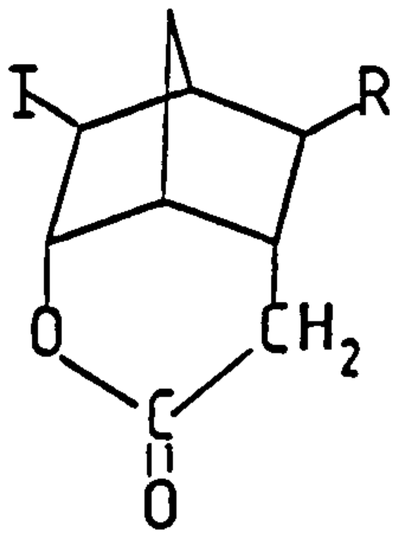
(185)

TABLE 20. ^{13}C nmr data for compound (171).

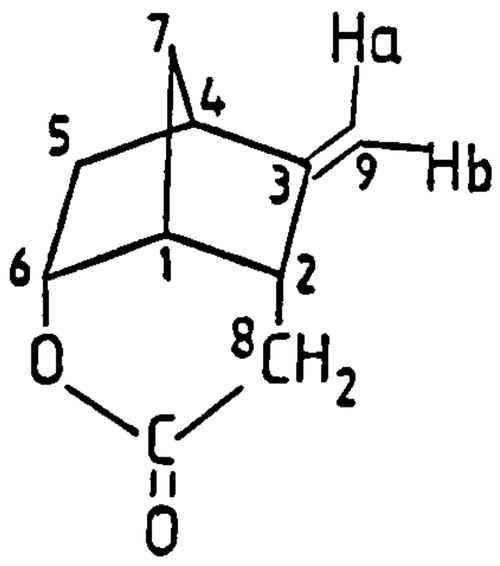
C	δ (ppm)	Multiplicity
C-6	172.2	s
C-8	141.2	d
C-3	137.3	d
C-9	133.9	s
C-11	130.8	d
C-12	130.1	d
C-7	129.5	s
C-10	128.9	d
C-4	128.1	d
C-2	87.0	d
C-5	39.6	t
C-1	39.4	d

2.4.2.0. Reaction of 6-endo-hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylcarboxylic acid δ-lactone (133) and 6-endo-hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo-ylcarboxylic acid δ-lactone (134) with silver tosylate.

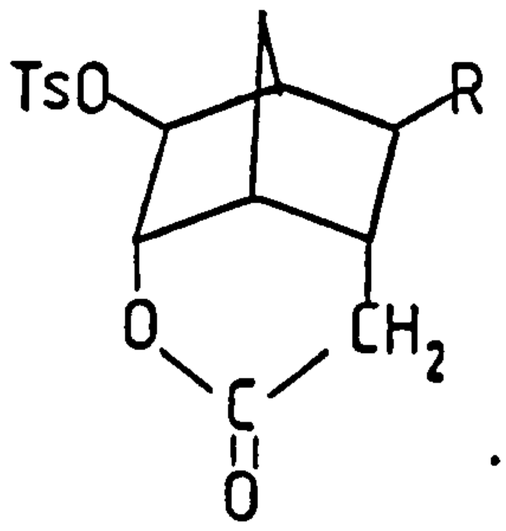
2.4.2.1. Scheme 20



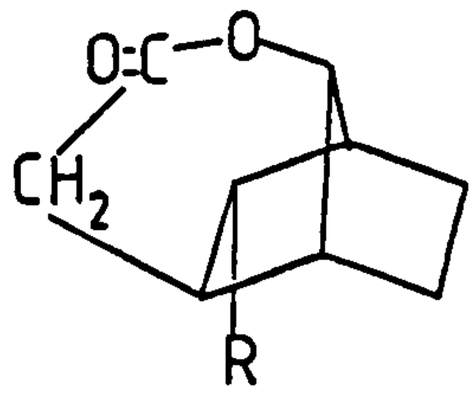
(132) R = H
(133) R = Me
(134) R = Ph



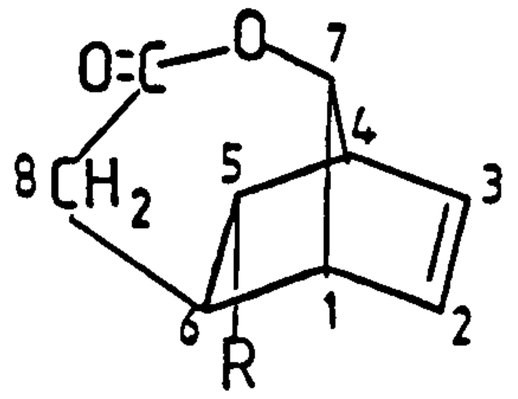
(189)



(188) R = Me
(191) R = Ph



(186) R = H
(187) R = Me
(190) R = Ph



(192) R = Ph

Reaction of the iodoδ-lactone (132) with silver tosylate leading to the rearranged product tosyloxyδ-lactone (186) has been reported.[142] The pathway for the formation of (186) seems to be identical with that for the tosyloxyγ-lactone (166) reported earlier (Section 2.4.1.2.) in the analogues reaction with the iodoγ-lactone (122). The iodoδ-lactone (133) when subjected to reaction with silver

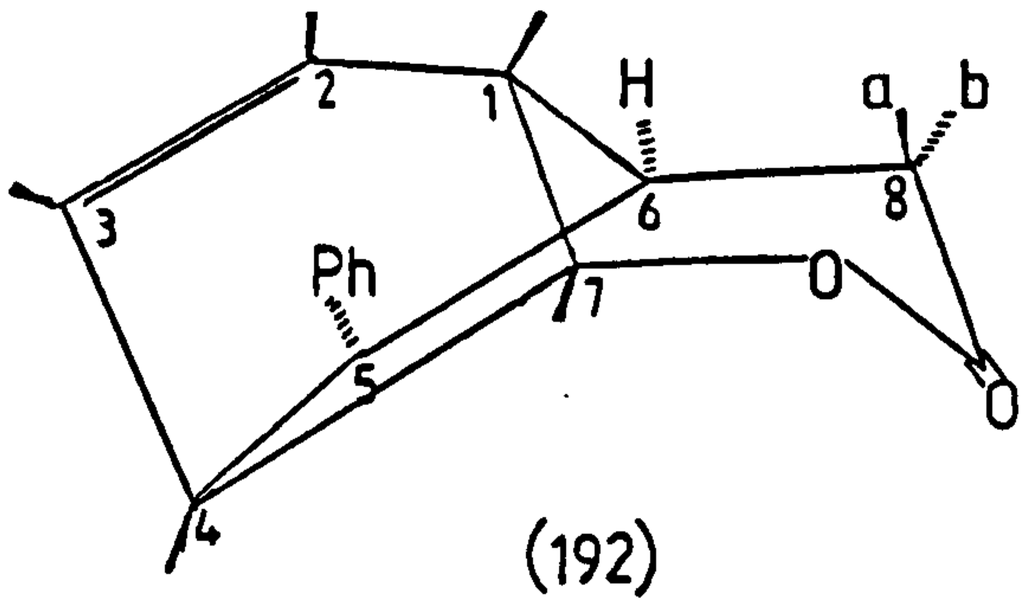
tosylate, by stirring for 16 h, afforded a crude product shown by t.l.c. to consist of three compounds. Purification by p.l.c. with 2:3 ethyl acetate/light petroleum b.p. 60-80^{o} as the eluent gave the compounds (187) R_F0.33, (188) R_F0.27 and (189) R_F0.47 isolated in 1:1.4:3.3 molar ratio. In addition to the tosyloxy δ-lactones (187) and (188) anticipated on the basis of the results with the iodoγ-lactone (127), the unsaturated δ-lactone (189) was formed as the major product. All the three compounds (187) - (189) exhibited similar strong absorptions at 1735 cm^{-1} (>C = O of a δ-lactone) in the infrared . The structures of (187) and (188) were determined with the help of spin-decoupling ^{1}H nmr experiments reported in Table 21; the ^{1}H nmr showed a d at δ7.70 and 7.75 (ortho-Aromatic), a d at δ7.33 and δ7.35 (meta-Aromatic), a d at δ4.58 and a brs at δ4.72 (>CH-OTs), a brs at δ4.27 and a q at δ4.80 (>CHO-) respectively. The unsaturated δ-lactone (189) contained a d at δ5.05 (olefinic proton 9a) and a d at δ4.82 (olefinic proton 9b) with J(9a,9b) = 2 Hz. Comparison with the published nmr spectrum of 2-methylenenorbornane,[143] for which the methylenic protons are found at δ4.90 and 4.64 respectively, indicated that the chemical shift of (9a) and (9b) were consistent with the structure (189). A m at δ4.90 (>CHO-) and a dxq at δ2.22 (H-5exo) with J(5-exo, 5-endo) = 14, J(5-exo, 6-exo) = 10 and J(5-exo, 4) = 4 Hz gave further support to (189). In an extension to the above investigation, the iodoδ-lactone (134) was also subjected to the same reaction with silver tosylate. After heating at 55^{o} for 16 h the reaction was complete,

and on work up, gave a mixture of 3 products; t.l.c. showed three spots at R_F0.58, 0.39 and 0.26 (2:3 ethyl acetate/light petroleum b.p. 60-80°). On separation by column chromatography, the compounds (192) R_F0.58, (190) R_F0.26, and (191) R_F0.39 were isolated in 1:3:4 molar ratio.

All the three compounds (190), (191) and (193) gave ir spectra exhibiting strong absorption at 1738, 1734 and 1735 cm^{-1} respectively (characteristic of δ-lactones). The compounds (190) and (191) were the major products and were readily identified by the ^1H nmr with the help of spin decoupling experiments (Table 21). The spectra of (190) and (191) showed respectively a d at δ7.46 and 7.80 (ortho-Aromatic), a d at δ7.30 and 7.32 (meta-Aromatic), a brd at δ4.92 and 4.69 (>CH-O-), a t at δ4.02 and a brs at δ4.42 (>CH-OTs), and a s at δ2.43 and 2.44 (p-CH_3). The minor product was the unsaturated γ-lactone (192) easily recognised by comparison with the unsaturated γ-lactone (171) which had previously been obtained from the iodoγ-lactone (128). A multiplet centred at δ7.20 integrating for five protons was assigned to the aromatic protons of the phenyl group. The olefinic protons appeared as a q at δ6.24 (H-2) and a q at δ5.77 (H-3). A d at δ4.33 (>CHO-) and a dxq at δ2.85 (CH_2CO) were consistent with the structure (192).

The spectrum of (192) showed overlapping quartets centres at δ2.85 due to H-8a and δ3.0 and H-8b at δ2.71 with J(8a,8b) = 17 Hz and J(8a,6-endo) = J(8b,6-endo) = 4 Hz; this suggests the lactone ring of

the unsaturated δ-lactone (192) had a chair conformation. This assumption is made on the basis of the Karplus equation[127] which showed a coupling constant of H-6endo with H-8a and H-8b of (3 Hz each), and (7 and 1 Hz) for a chair and a boat conformation respectively.

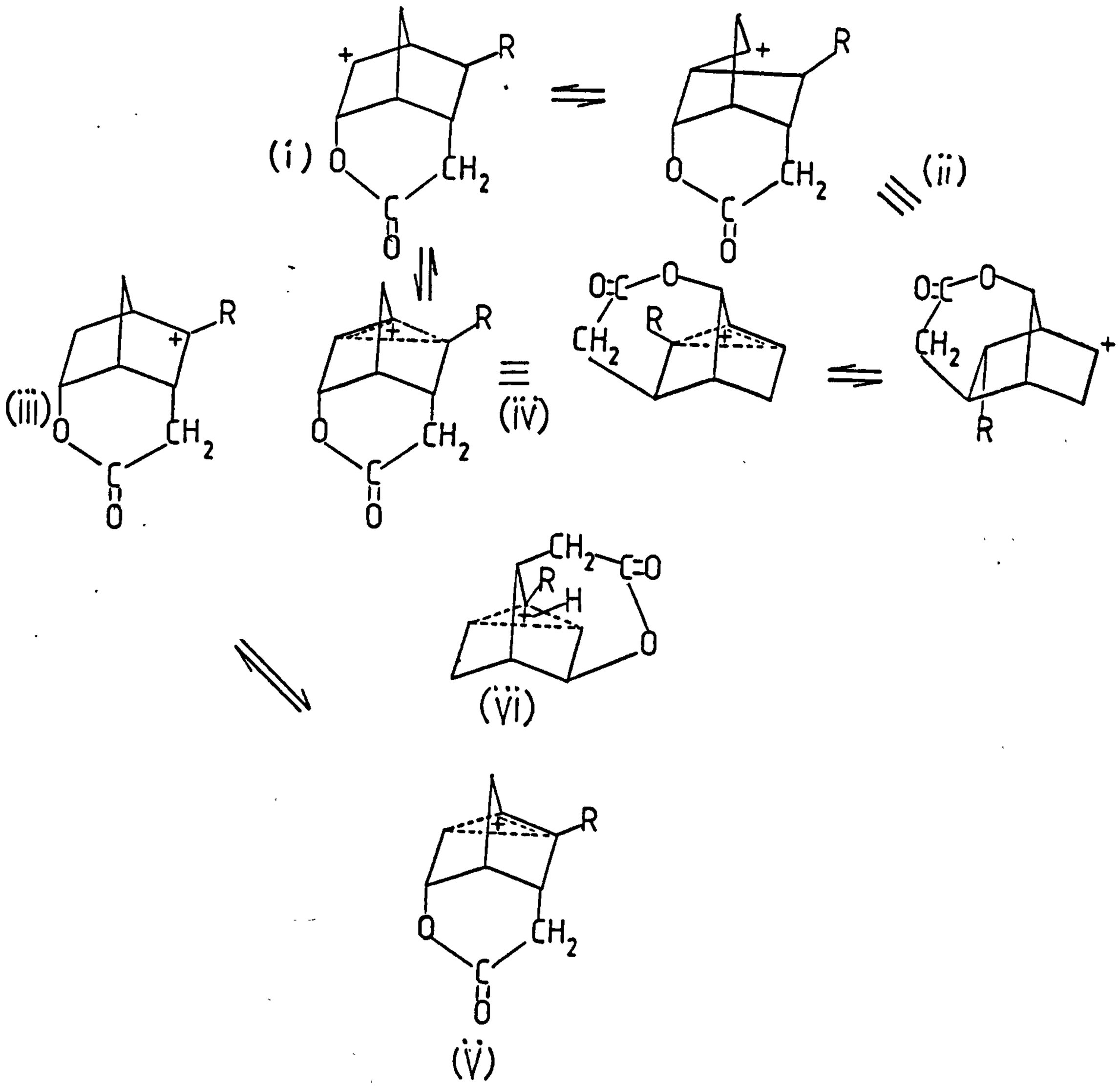


(192)

This evidence further supports the first proposals of the chair conformation reported for the lactone ring in the iodoδ-lactones (133) and (134).

Ionisation of the iodoδ-lactones (133) and (134) leads to the carbocation I(R = Me, Ph) in Scheme 21, which if captured by tosyloxy ion would give (188) and (191) respectively. Alternatively I(R = Me, Ph) may undergo a Wagner-Meerwein rearrangement to carbocation II(R = Me, Ph), for which (187) and (190) are derived. In II when R = Ph, beside the product (190) being formed from II, abstraction of a proton by tosyloxy ion acting as a base also takes place to give (192). The formation of the unsaturated δ-lactone (189) as the major product from the iodoδ-lactone (133) requires an alternative route. The carbocation I(R = Me) may undergo 3,5-endo,endo

Scheme 21



hydride shift[64,82b] to give the more stable tertiary carbocation III(R = Me). The cation (III) was not captured by tosyloxy ion to give products, probably due to steric hindrance by methyl group, and instead loss of a proton from methyl group took place to give product (189). Instead of the classical carbocations (I) - (III), product formation is also explicable <u>via</u> the non-classical carbocations (iv) and (v), for which (vi) was a composite.

TABLE 21. <u>Spin-decoupling experiments for the compounds (187) - (192)</u>.

Compounds	Irradiated proton	δ	Observations
187	H-7<u>anti</u>	4.27	Sharpening of a m at δ1.70 of H-6<u>endo</u> and H-5<u>exo</u> and H-2<u>exo</u>.
	H-6<u>endo</u>, 2-<u>exo</u> and H-5<u>exo</u>	1.70	Sharpening of a brs at δ4.27 of H-7<u>anti</u>, and a brd at δ4.85 to d; J(3<u>endo</u>, 2<u>endo</u>) 5Hz, collapse a d at δ2.54 of H-8a and H-8b to s.
188	H-6<u>exo</u> and H-5<u>endo</u>	4.75	Sharpening of a m centred at 1.95 of H-1, H-7<u>anti</u> and H-7<u>syn</u>.
	H-8a, H-8b	2.57	Collapse of a m at δ1.53 of H-2<u>exo</u> to brt; J(2<u>exo</u>, 1) 3Hz and J(2-<u>exo</u>, 3-<u>endo</u>)3 Hz.
	H-2<u>exo</u>	1.53	Collapse of a d at δ2.57 of H-8a, 8b to a s, sharpening of a m at δ2.13 of H-1 and a brd at δ1.82 to d; J(3<u>endo</u>, CH_3)8 Hz.
	CH_3	1.0	Collapse of a brd at δ1.82 of H-3<u>endo</u> to brs.

... Cont'd ...

TABLE 21. (Continued)

Compounds	Irradiated proton	δ	Observations
189	H-6exo,H-9a and H-9b	4.90	Collapse of a dxq at δ2.22 of H-5exo to dxd; J(5-exo,5-endo)14 and J(5-exo,4)4 Hz, collapse of a dxt at δ1.40 of H-5endo to dxd. J(5-endo, 5-exo)14 and J(5-endo,7-anti) 3 Hz.
	H-5exo	2.22	Sharpening of a m at δ4.90 of H-6exo, collapse of a dxq at δ1.53 to brs of H-5endo, and sharpening of a m of H-4 at δ2.75.
190	H-2exo, H-2endo	1.89	Collapse of a brt at δ4.02 of H-3endo to brs, and sharpening of a brs at δ2.29 of H-1.
	H-5exo	3.15	Collapse of a brd at δ2.77 of H-4.
	H-7anti	4.92	Collapse of a d at δ2.49 of H-6endo.
	H-3endo	4.02	Collapse of a m at δ2.89 of H-2exo and H-2endo to brs.
191	H-7anti H-7syn	1.97	Sharpening of a brs at δ4.42 of H-5endo and a m at δ2.48 of H-1 and H-4.
	H-6exo	4.69	Collapse of a m at δ2.48 of H-1 to brs.
192	H-7syn	4.33	Sharpening of a brm at δ2.39 of H-6endo to a brd; J)6-endo,8a)4 Hz.
	Ph	7.20	no changes.
	H-2	6.24	Collapse of a q at δ5.77 of H-3 to brs.
	H-3	5.77	Collapse of a q at δ6.24 to d; J(2,1)4 Hz.

... Cont'd ...

TABLE 21. (Continued)

Compound	Irradiated proton	δ	Observations
192	H-5exo,H-4	3.25	Collapse of a q at δ5.77 of H-3 to d; J(3,2)6 Hz, collapse of a brd at δ4.33 of H-7syn to t; J(7-syn,1)3 and J(7-syn, 6-endo)3 Hz. Collapse of a m at δ2.39 of H-6endo to q; J(6-endo,8)4 Hz and J(6-endo, 7-syn)3 Hz.
	H-6endo	2.39	Collapse of a dxq at δ2.85 to q; J(8a, 8b)17 Hz.

TABLE 22. ^{1}H nmr data for compounds (187) - (192).

Compound	δ (ppm)													
	1	2-exo	2-endo	3-exo	3-endo	4	5-exo	5-endo	6-exo	6-endo	7-syn	7-anti	ortho	meta	8a,8b
187	m 2.10	m 1.70			d 4.58	brs 2.42	m 1.70	d 1.0		m 1.70		brs 4.07	d 7.80	d 7.33	d 2.54
188	m 2.13	m 1.53		d 1.0	d 1.82	brs 2.42		d 4.72	q 4.80		m 1.90		d 7.75	d 7.35	d 2.57
189	m 2.75	m 2.54				m 2.75	dxq 2.22	dxt 1.40	m 4.90		m 1.57				d 2.75
190	brs 2.29	m 1.89			t 4.02	d 2.77	d 3.15	m 7.11		d 2.49		brd 4.92	d 7.46	d 7.30	brd 2.66
191	m 2.36	m 2.32		m 7.22	br 2.66	m 2.57		brs 4.42	d 4.69		m 1.97		d 7.80	d 7.32	brd 2.66
192	brs 2.78	q 6.24		q 5.77		m 3.25		m 7.20		m 2.39	d 4.33				dxq 2.85

A s at δ2.44 for p-CH_3 (187-192).

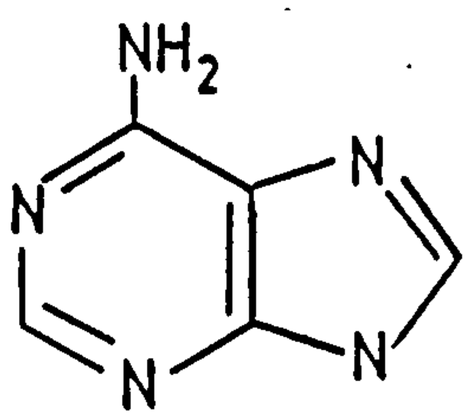
A d at δ5.05 (9a) and a d at δ4.82 (9b) in (189).

3.0.0.0. CHAPTER 3. SYNTHESIS OF MODIFIED C-NUCLEOSIDES.

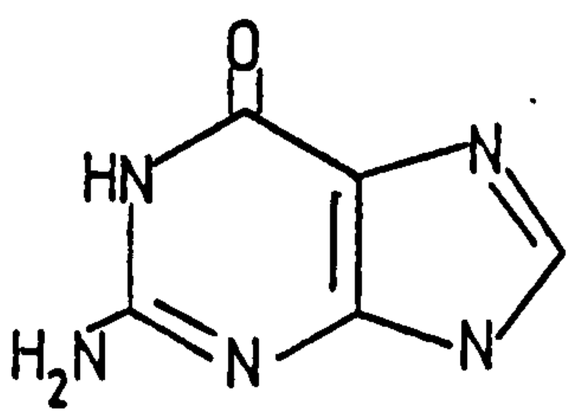
3.1.0.0. Introduction.

The term C-nucleoside is used to describe chemical compounds in which a heterocyclic base is linked to the C-1 of a sugar by a carbon-carbon bond instead of by a carbon-nitrogen bond as is found in normal nucleosides.

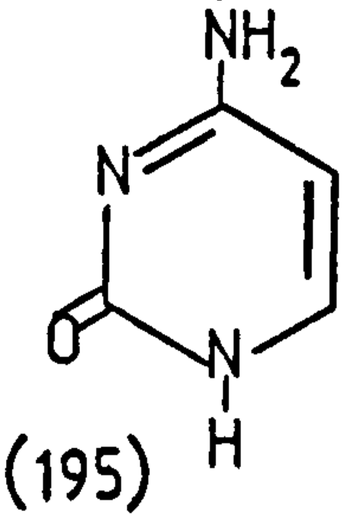
In general nucleosides, which consist of nitrogenous heterocyclic bases such as purine, pyrimidine and their derivatives, together with a sugar are obtained by the mild hydrolysis of nucleic acids. The most common heterocyclic bases found are adenine, abbreviated (A) (193), guanine (G) (194), cytosine (C) (195), thymine (T) (196), and uracil (U) (197); the sugar residue is either D-ribose or 2-deoxy-D-ribose.



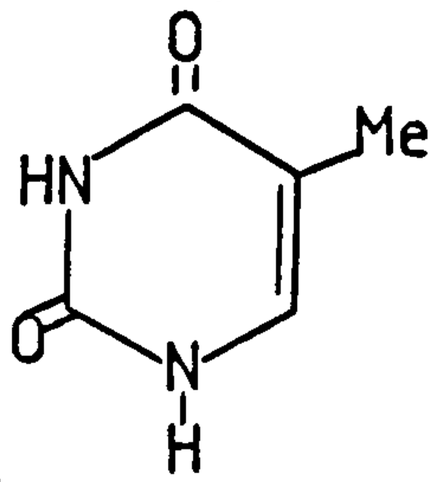
(193)



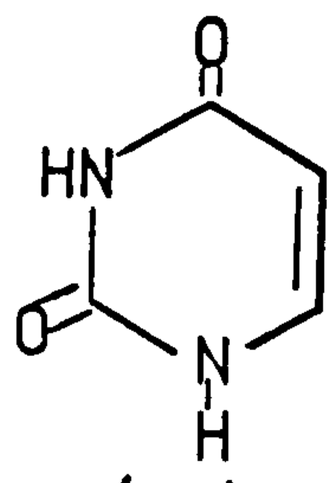
(194)



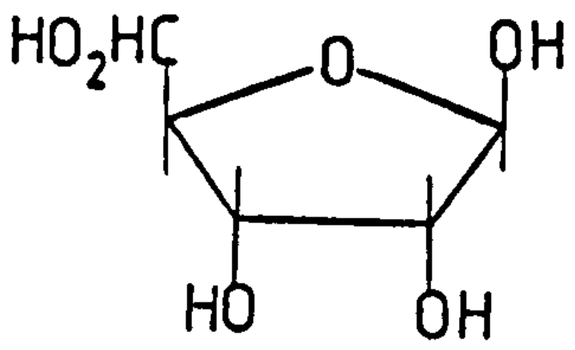
(195)



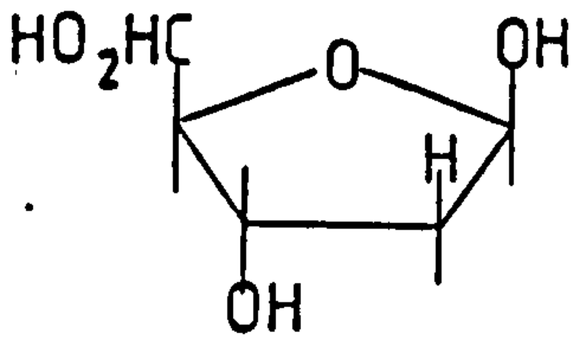
(196)



(197)

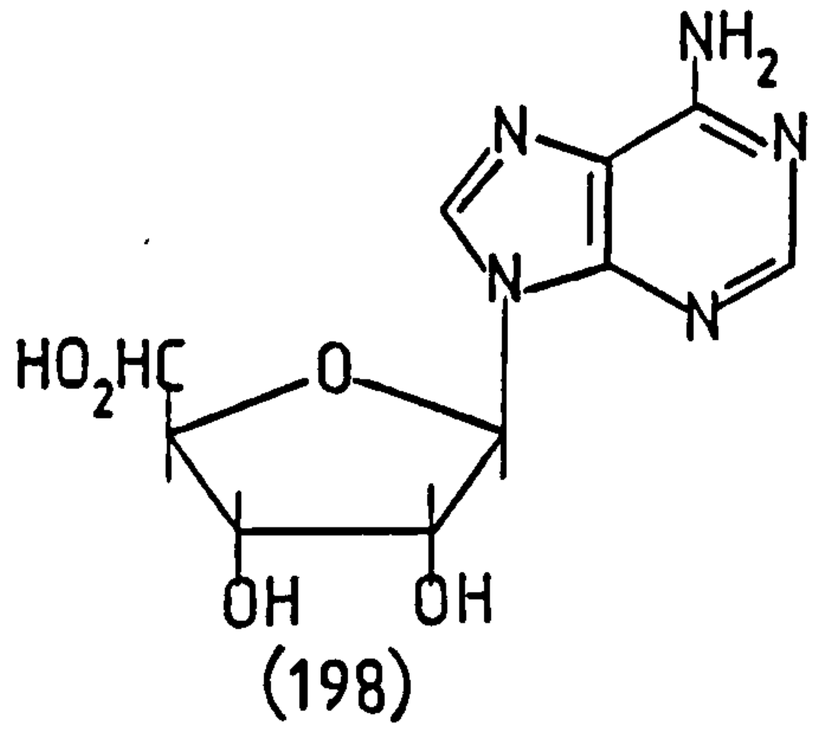


D-Ribose



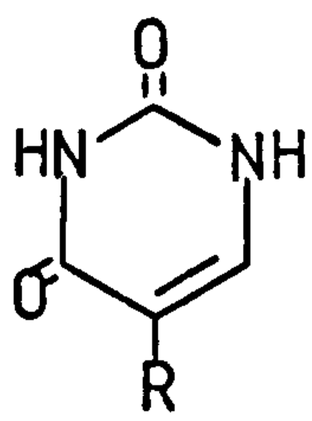
2-Deoxy-D-ribose.

The link of the base to the sugar normally has the β-configuration such as for example the structure of adenosine (198).

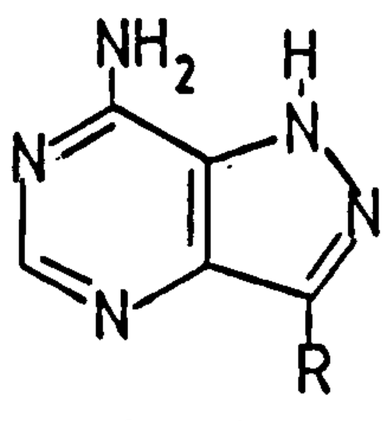


(198)

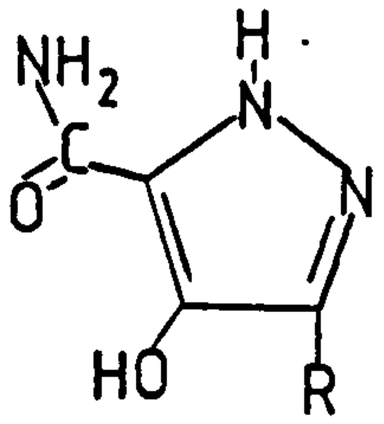
3.1.1.1. The first C-nucleoside to be discovered was 5-β-D-ribofuranosyluracil (199) obtained by Cohn[144] during fractionation of transfer RNA. Other naturally occurring C-nucleosides since discovered include the biologically active formycin A (200),[145] showdomycin (201),[146] pyrazomycin (202)[147] and oxazinomycin (203).[148]



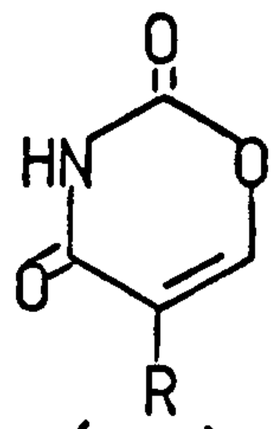
(199)



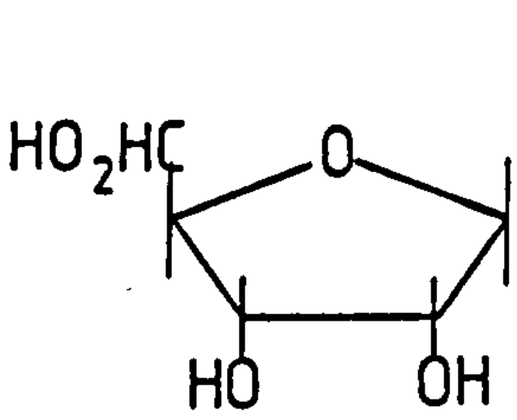
(200)



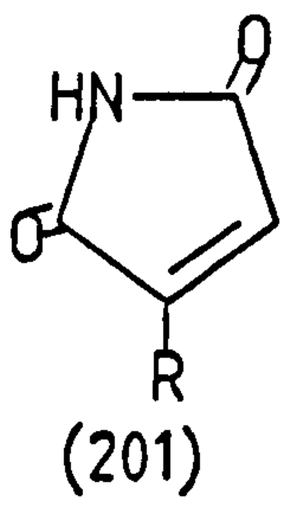
(202)



(203)



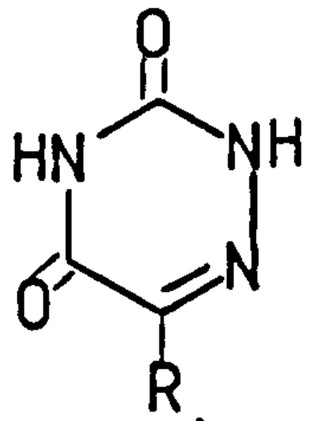
= R



(201)

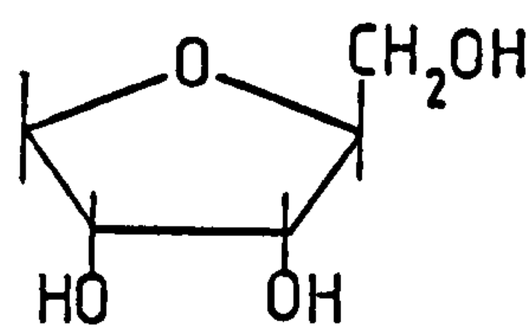
3.1.1.2. Previous studies have shown that some heterocyclic bases have biological activity e.g. 6-azauracil (204a) possesses narcotic activity,[149,150] and caused a variety of disturbances to the central nervous system in man.[151]

Even greater activity was reported[152] for the 5-alkyl derivatives (204) of 6-azauracil. The activity sequence decreases along the series, R = n-C_7H_{15}; n-C_5H_{11}, -$CH(CH_3)_2$, n-C_3H_7, -C_2H_5, -CH_3, and H.



(204)

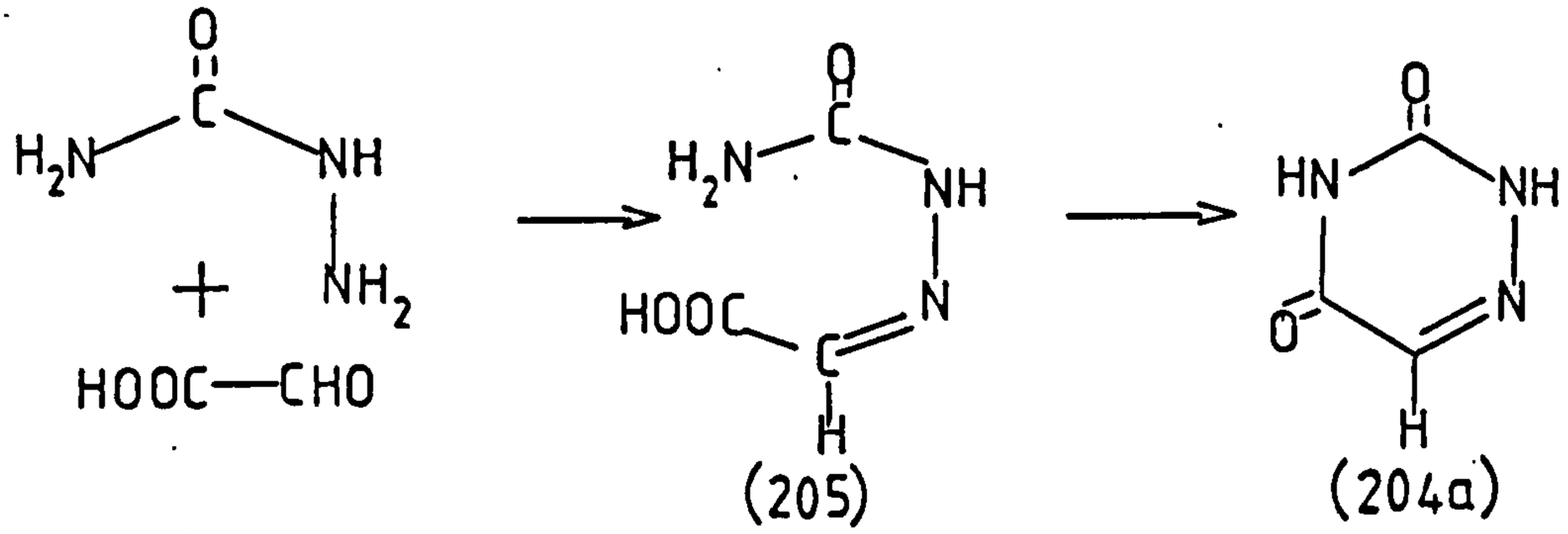
(204a) R = H
(204b) R = CH_3
(204c) R = C_2H_5
(204d) R = n-C_3H_7
(204e) R = $CH(CH_3)$
(204f) R = n-C_5H_{11}
(204g) R = n-C_7H_{15}
(204h) R =



Prusoff[153] also reported that 5-methyl-6-azauracil (204b) was marked by more active than 6-azauracil (204a) as an inhibitor of the growth of Streptococcus faecalis, Lactobacillus leichmannii and Thermobacterium acidophilum. Interest in the biological activity of 6-azauracil led to the examination by Bobek[153] of the C-nucleoside of 5-(β-D-ribofuranosyl)-6-azauracil (204h).

3.1.2.0. Synthesis of the heterocyclic base 6-azauracil.

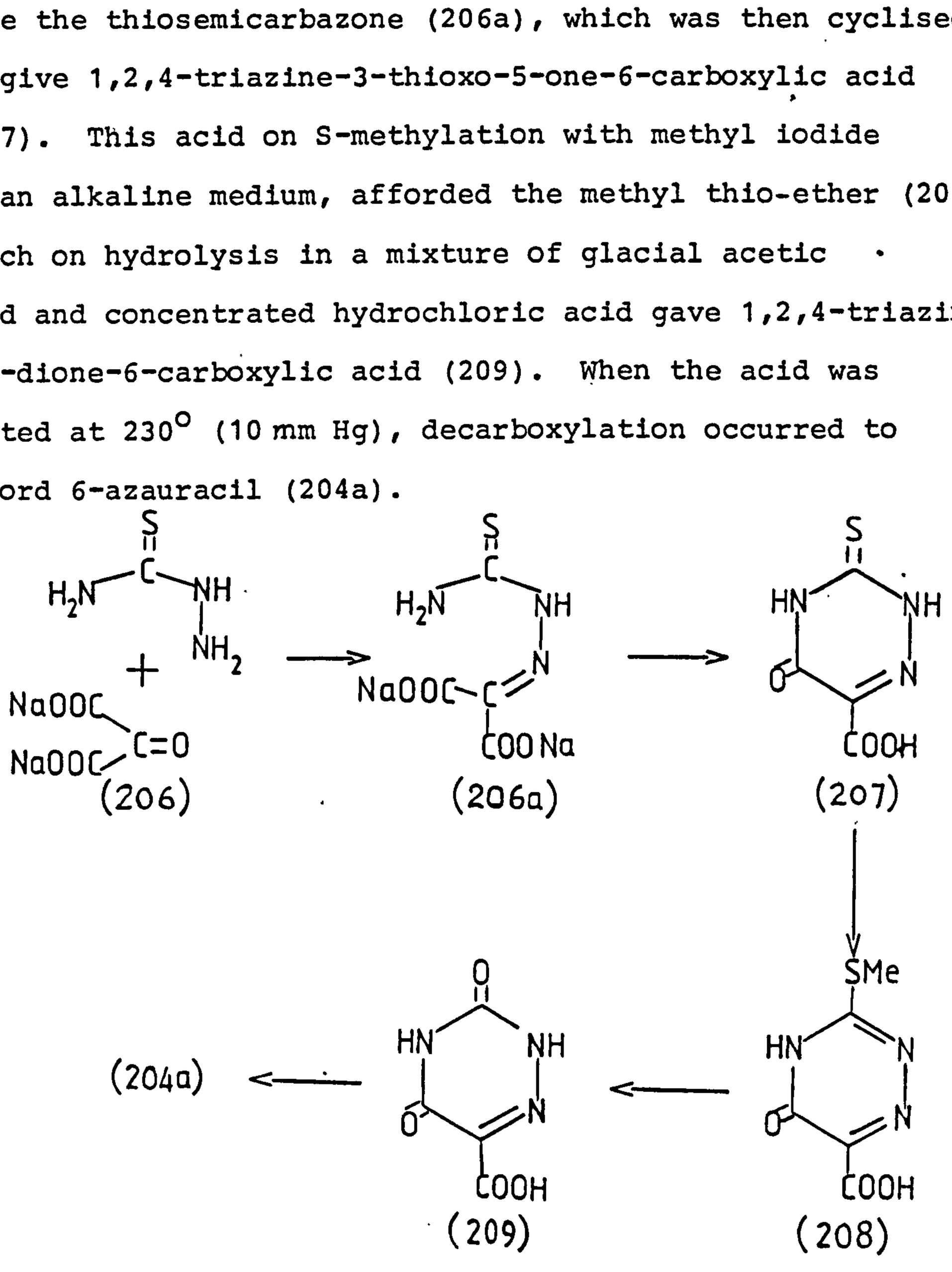
3.1.2.1. Seibert[154] first synthesised 6-azauracil (1,2,4-triazine-3,5-dione) (204a) by initially preparing the semicarbazone of glyoxylic acid (205) (from the condensation of semicarbazide with glyoxylic acid) and then cyclising this product in alkaline medium.



(205)

(204a)

Subsequently Barlow[155] discovered that thiosemicarbazide condensed readily with sodium mesoxalate (206) (in preference to condensation with the free acid) to give the thiosemicarbazone (206a), which was then cyclised to give 1,2,4-triazine-3-thioxo-5-one-6-carboxylic acid (207). This acid on S-methylation with methyl iodide in an alkaline medium, afforded the methyl thio-ether (208), which on hydrolysis in a mixture of glacial acetic acid and concentrated hydrochloric acid gave 1,2,4-triazine-3,5-dione-6-carboxylic acid (209). When the acid was heated at 230° (10 mm Hg), decarboxylation occurred to afford 6-azauracil (204a).



(206)

(206a)

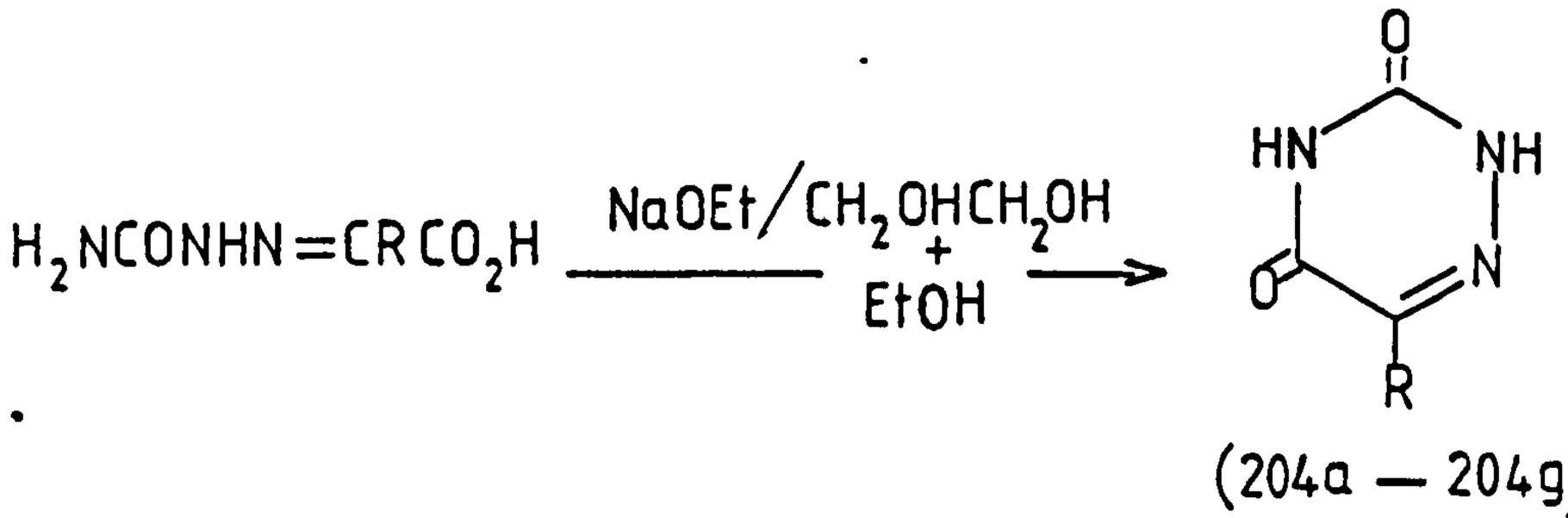
(207)

(208)

(209)

(204a)

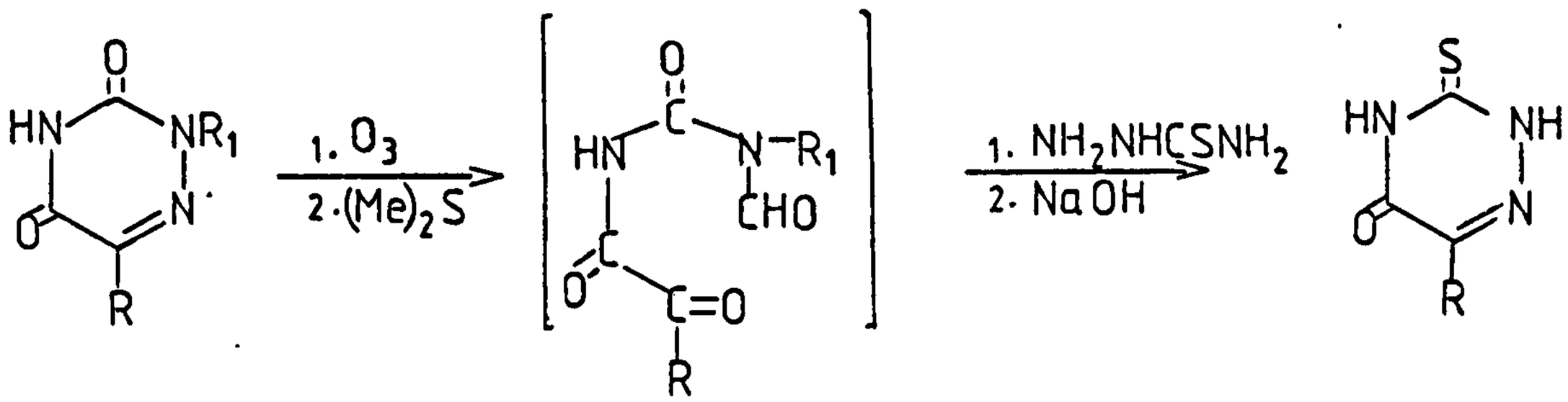
3.1.2.2. An unsuccessful procedure of Bailey[156] and Bougault[157] for the cyclisation of the semicarbazone of pyruvic acid, was successfully modified by Chang,[158] who used instead of aqueous sodium hydroxide as base a mixture of ethylene glycol and absolute alcohol containing sodium. This was applicable to the synthesis of 5-alkyl-6-azauracil (204b-204g) from the semicarbazones of the corresponding α-keto acids in average yields of 50% to 94%. For example the semicarbazone of pyruvic acid gave 5-methyl-6-azauracil (204b) in a yield of 51%.



(204a — 204g)

3.1.2.3. Bobek et al.,[159,160] were successful in their attempt to synthesise 6-azapseudouridine [5-(β-D-ribofuranosyl)-6-azauracil] (204h) with the aid of the model compounds 1-acetylthymine (210a) and 1-acetyl-5-methoxymethyluracil (210b). They succeeded in cleaving the carbon-carbon double bond linkage of (210a;b), by ozonolysis in methanolic solution at -40° followed by reduction of the resulting ozonide with dimethylsulphide using the method of Pappas and Keaveney,[161] to give an unisolated product of probable structure (211a and 211b). Treatment of the intermediate (211a) and (211b) with thiosemicarbazide and subsequent ring closure in alkaline media afforded 6-methyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (212a) (37%) and 6-methoxymethyl-3-thioxo-

2,3,4,5-tetrahydro-1,2,4-triazine-5-one (212b) (42%).

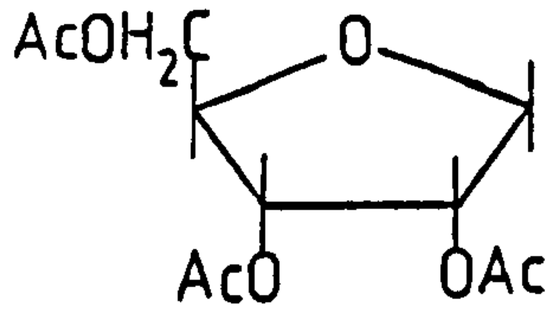


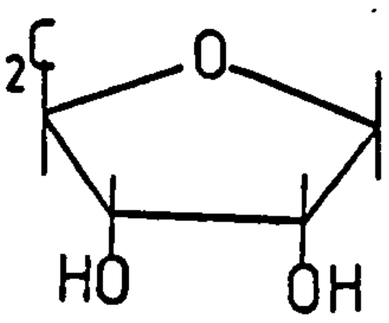
(210) (211) (212)

(210a — 211a) R = Me; R_1 = Ac. (210b — 211b) R = CH_2OMe; R_1 = Ac.

(212a) R = Me. (212b) R = CH_2OMe.

(210c — 211c) R = ; R_1 = H. (212c) R = .

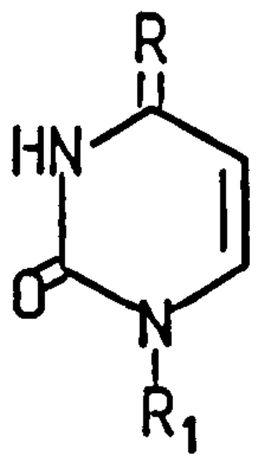




The method was applicable to the conversion of 2',3',5'-tri-O-acetylpseudouridine (210c) to (204h) following ozonolysis of (210c) at -65° and reduction with dimethyl-sulphide to (211c). Condensation of the intermediate (211c) with thiosemicarbazide and subsequent ring closure afforded 6-β-D-ribofuranosyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (212c) in a 28% yield. On S-methylation of (212c) with methyl iodide in an aqueous medium and subsequent acid hydrolysis 5-(β-D-ribofuranosyl)-6-azauracil (204h) was obtained in 76% yield.

3.1.3.0. <u>Examples of the conversion of C=S bond to C=O bond in heterocyclic compound</u>.

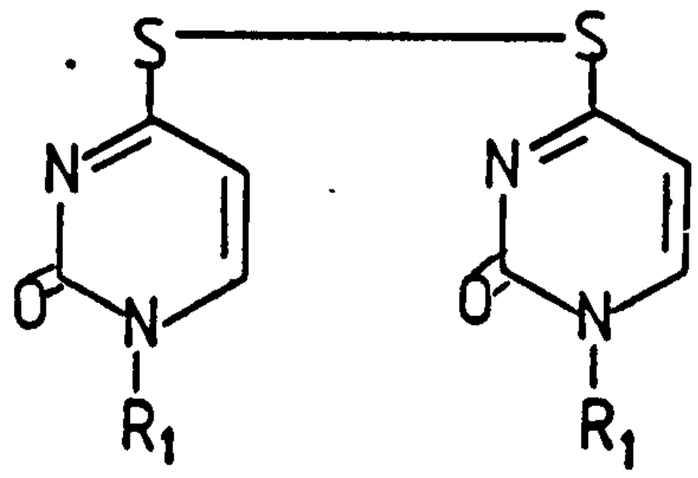
3.1.3.1. Walker[162,163] reported that the reaction of 4-thiouridine (213) with an excess of cyanogen bromide at pH = 8.5 in a phosphate buffer at 100° for 3 min afforded uridine (216) and 4-thiouridine (213) in (7:3) ratio.



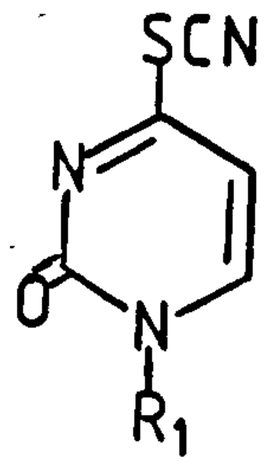
(213) R=S

(216) R=O

R_1 = ribosyl



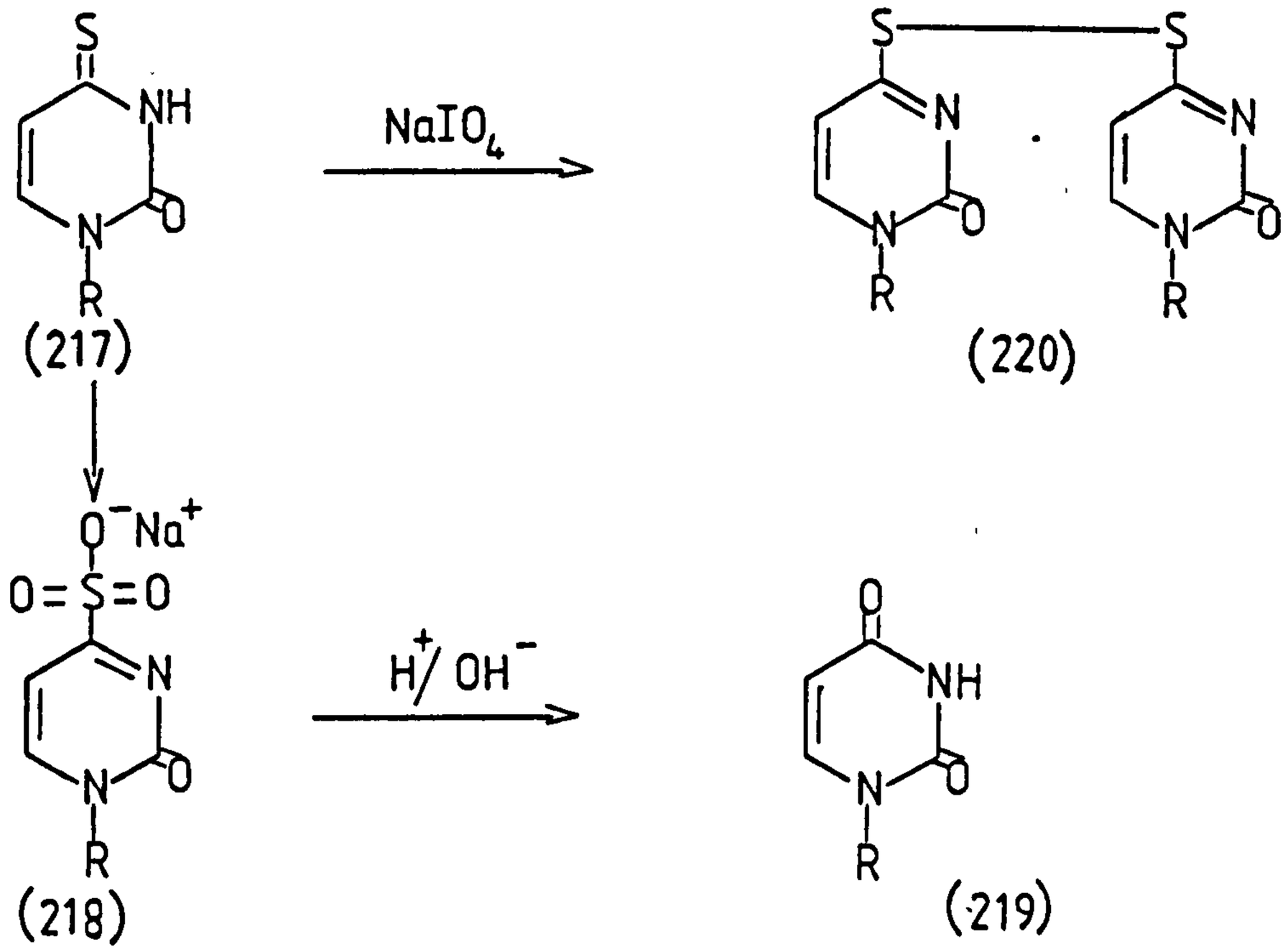
(214)



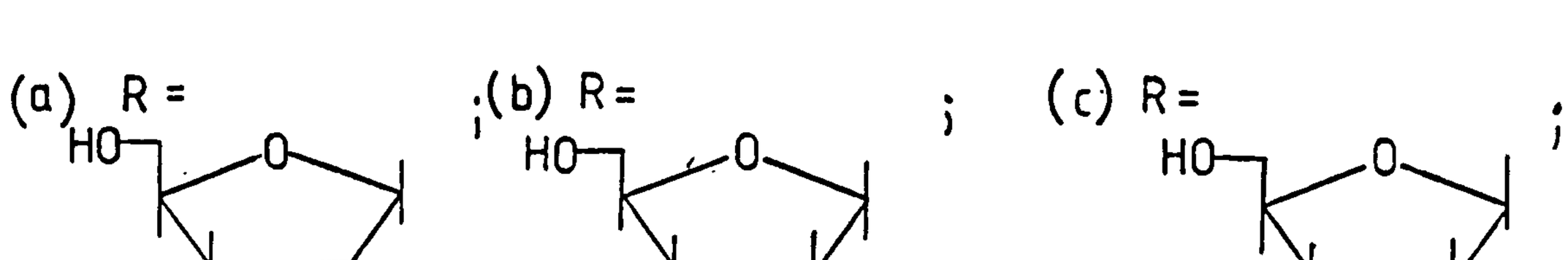
(215)

Variation in pH and the use of other types of buffer solution adversely affected product formation. For example if ammonium bicarbonate buffer was used, cystidine was produced together with some uridine and other unidentified compounds. The pathway of the reaction involved the formation of the disulphide (214) when cyanogen bromide reacted with 4-thiouridine at pH 6.5. The disulphide on further addition of cyanogen bromide, followed by heating at 37°, afforded a mixture of 4-thiouridine (213) and 4-thiocyanatouridine (215). The reaction occurred more rapidly when the pH was increased to pH 8.5, and the thiocyanate (215) decomposed to uridine (216) when heated at 100° for 3 min.

3.1.3.2. Oxidation of 4-thiouridine nucleosides with suitably protected pentose moieties in low concentration in aqueous medium at pH 7 (35°), and subsequent H^+ or OH^- hydrolysis to give uridine nucleosides was well established by Ziff and Fresco.[164]. Thus 2'-deoxy-4-thiouridine (217a) and 2',3'-O-isopropylidene-4-thiouridine (217b) were oxidised with sodium periodate to 2-oxypyrimidine-4-sulphonate nucleoside (218). The sulphur substituent of (218) was identified as a sulfonic acid moiety on the basis of infrared [165] and its stability in the presence of a large excess of periodate, rather than a sulphinic acid, since sulphinic acids are readily oxidised to sulphonic acids in a variety of oxidising agents.[166]



(217) (218) (219) (220)



Hydrolysis by acid or base of the intermediate sulphonates afforded 2'-deoxyuridine (219a) and 1-(2',3'-isopropylidene-β-D-ribofuranosyl)-uridine (219b). The oxidation in high concentration of 4-thiouridine (217a) was reported to give a mixture of disulphide (220a) and the intermediate sulphonates (218a).

3.1.3.3. Irradiation[167] of 1-(2',3'-β-D-ribofuranosyl)-4-thiouridine (217c) in air-saturated tertiary butanol with a mercury high pressure lamp filtered by a Pyrex filter or with monochromatic light at 330 mu gave the uridine (219c) in a quantitative yield. Detection of sulphide ions in the photolysis solution was considered evidence for the intermediate 1-(2',3'-β-D-ribofuranosyl)-2-oxypyrimidine-4-sulphonate (218c).

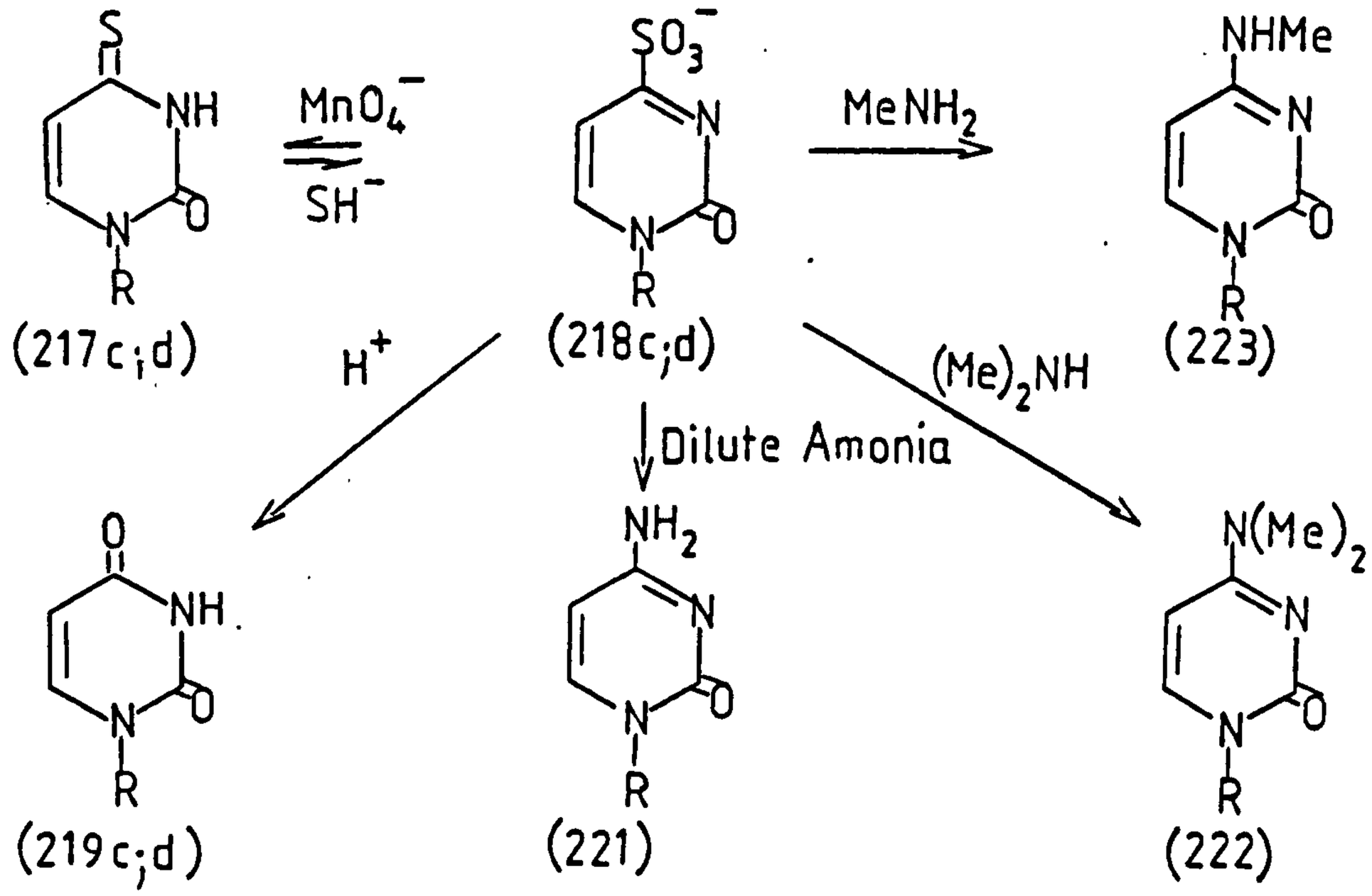
3.1.3.4. Yano and Hayatsu[168] reported that oxidation of 4-thiouridine nucleosides with potassium permanganate had one advantage compared to the periodate oxidation[164] because the hydroxy groups at C-2' and C-3' of the furanose ring were unaffected. The stoichiometry of the oxidation was followed as in reaction 1, in which two molecules of potassium permanganate were needed to oxidise one molecule of 4-thiouridine.

$$R\text{-}SH + 2KMnO_4 \longrightarrow RSO_3^-K^+ + 2MnO_2 + KOH \qquad -(1)$$

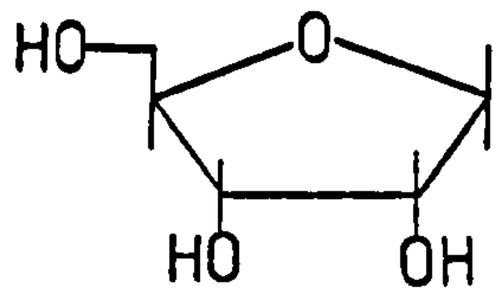
Thus oxidation of 4-thiouridine (217c) afforded an

intermediate of 2-oxypyrimidine-4-sulphonate (218c) and the presence of the sulphonate salt was strongly supported by the isolation of the sulphonate of the 1-methyl analogue (218d) during oxidation of 1-methyl-4-thiouridine (217d) as a crystalline salt. Acid hydrolysis of the intermediate sulphonates gave uridines (219c) and (29d). They[168] also found the intermediate uracil-4-sulphonates were highly reactive towards various nucleophilic reagents such as acid, dilute ammonia, methylamine, dimethylamine and hydrogen sulphide to give products such as in Scheme 22:

Scheme 22



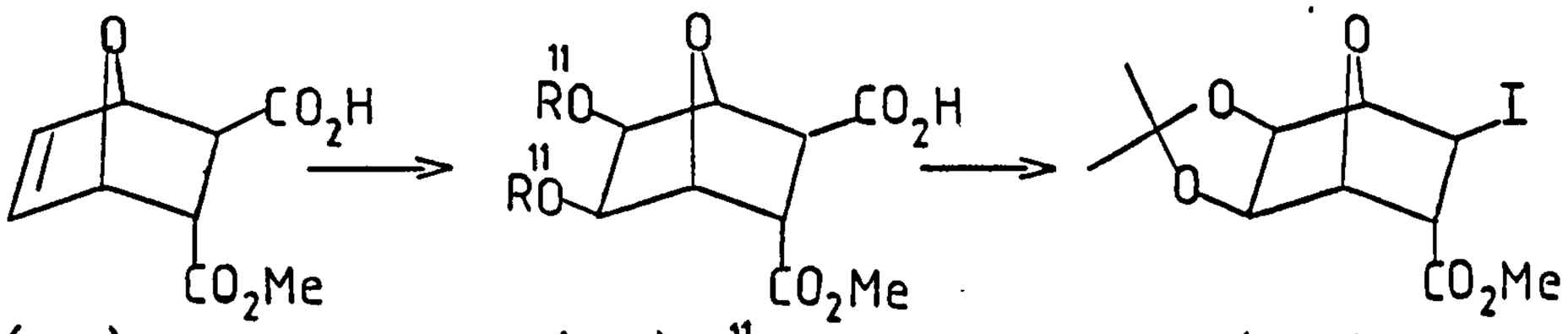
(217c — 219c ; 221 — 223) R =



(217d — 219d) R = Me

3.1.4.0. Synthesis of C-nucleoside intermediates from bicyclic systems .

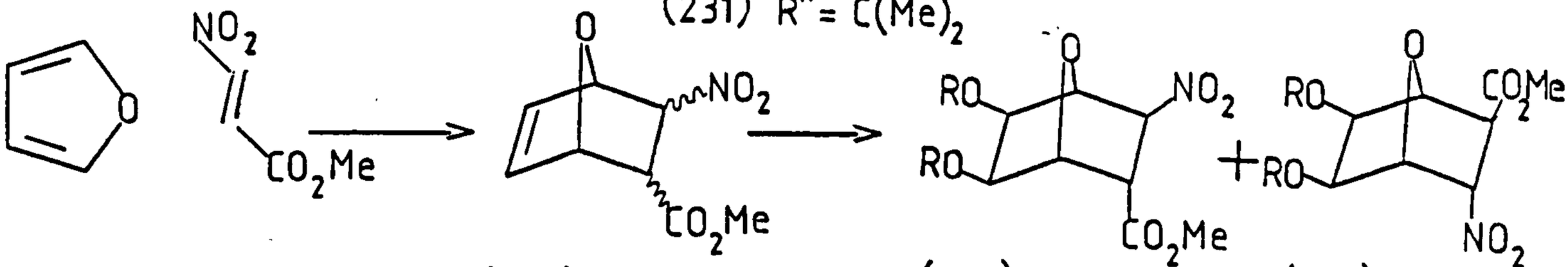
2.1.4.1. The synthesis of C-nucleoside required intermediates of type (224), (225),[169] (226) or (227)[170,171] were described by Just and Martell[172] who used the olefin (228) as a precursor for such intermediates. The olefin (228) was prepared by the hydroxylation of the adduct (229), obtained from furan and monomethylfumarate, to give the diol (230), which was protected by dimethoxy-propane to give (231). When the half acid (231) was subjected to photolysis in the presence of lead tetracetate and iodine,[173] crude iodo ester (232) was obtained, which was directly dehydroiodinated with DBU to the olefinic ester (228) in low yield. A second attempt was made by using the adduct of furan with methyl-nitroacrylate[174,175] to give a mixture of adduct (233). Hydroxylation with osmium tetroxide-hydrogen peroxide afforded a mixture of diols (234) and (235) which was treated with acetone-dimethoxypropane-TsOH to give (236) and (236a), which on treatment with DBU gave the olefin (228) in high yield. Oxidation of the olefin (228) with ruthenium oxide afforded the keto acid (224), which was characterised as the methyl ester (224a). Ozonolysis of (228) gave the ozonide (237), which was reduced with dimethylsulphide to the hemiacetal (238); reduction of (237) and (238) with sodium borohydride gave the triols (239) which on periodate oxidative cleavage afforded the required intermediate (225).



(229)

(230) R^{11} = H
(231) R^{11} = C(Me)$_2$

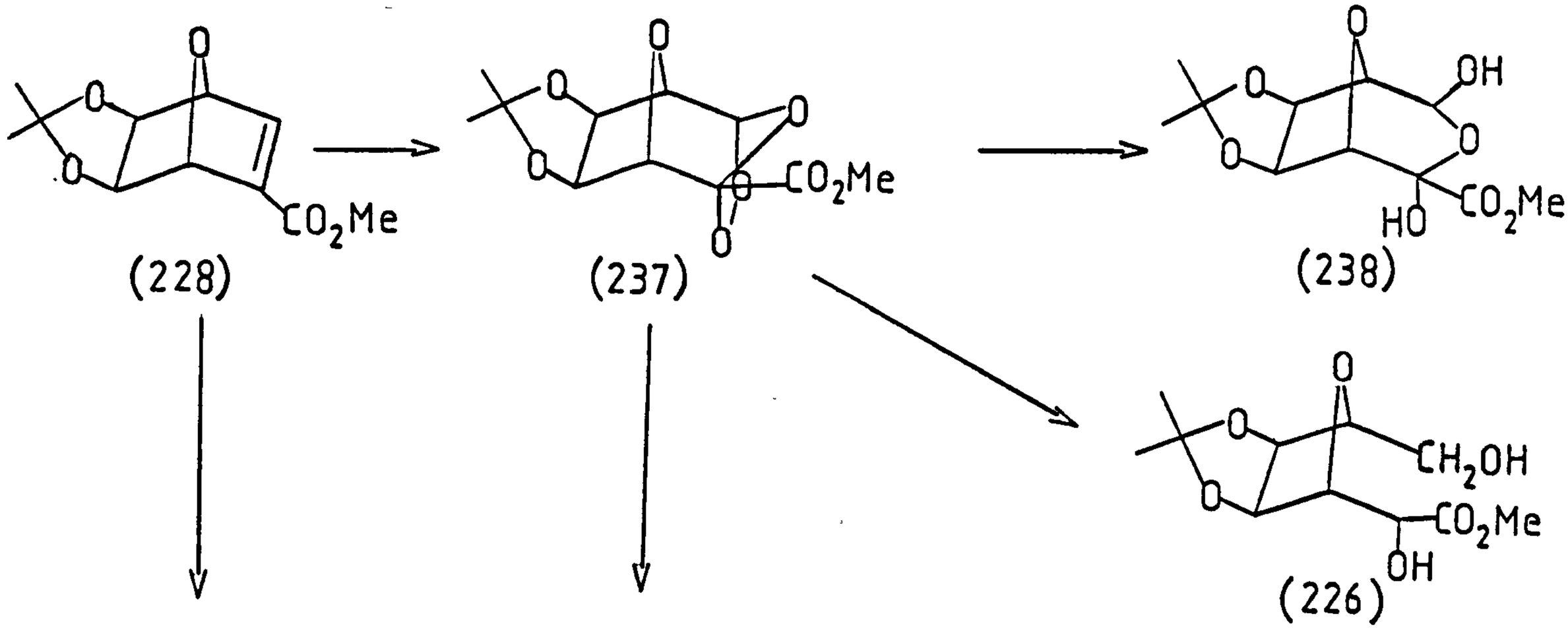
(232)



(233)

(234) R=H
(236) R=C(Me)$_2$

(235) R=H
(236a) R=C(Me)$_2$



(228)

(237)

(238)

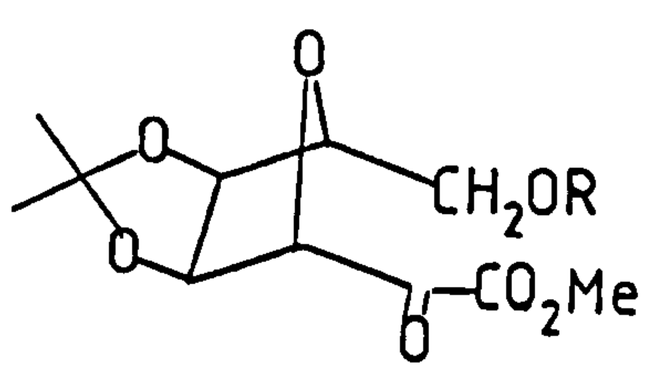
(226)

(224) R=H

(224a) R=Me

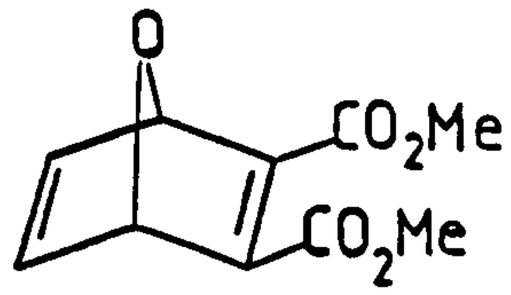
(239)

(225)

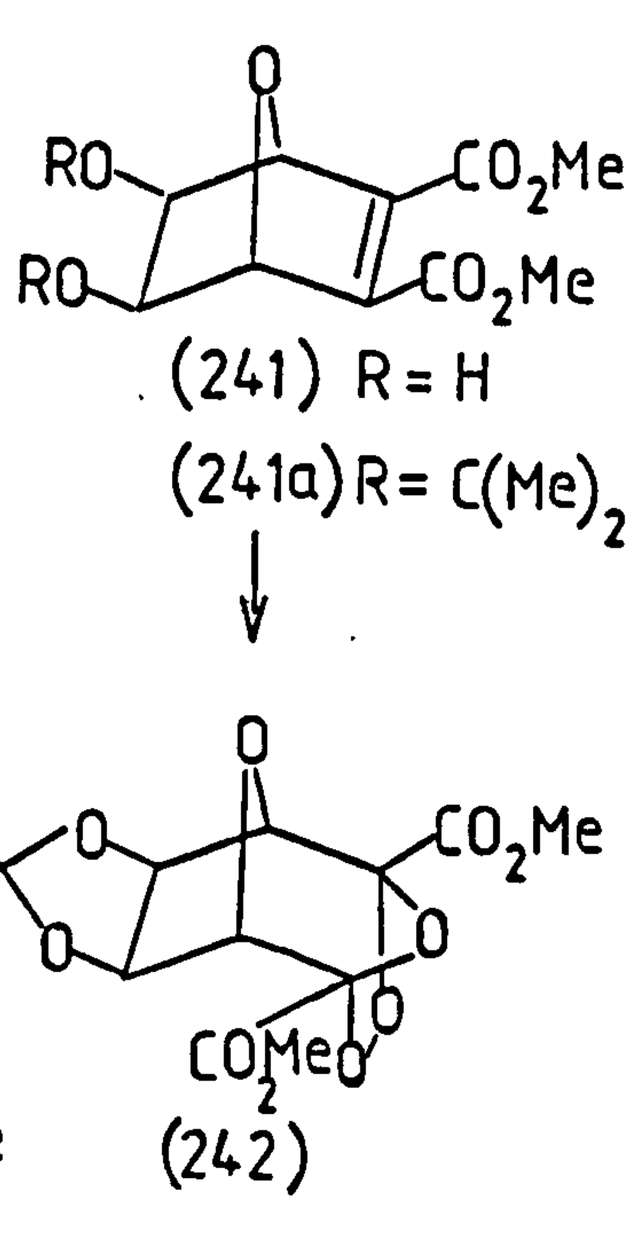


(227)

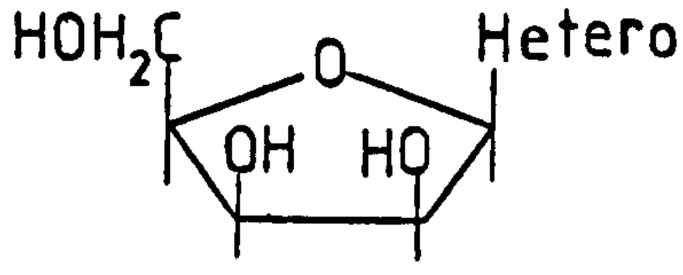
3.1.4.2. The intermediate (224) was also obtained by Just and Grozinger[176] from the adduct (240) of furan with dimethylacetylenedicarboxylate. Oxidation of (240) with osmium tetroxide gave the exo-diol (241) which was transformed to the corresponding isopropylidene derivative (241a) on treatment with acetone-dimethoxypropane-p-toluenesulphonic acid. Ozonolysis of (241a) gave the ozonide (242) which upon heating with solvents such as tetrahydrofuran gave the oxalic ester (243) (60%) and the keto-ester (224) (27%).



(240)



3.2.0.0. Aims and objectives of research.

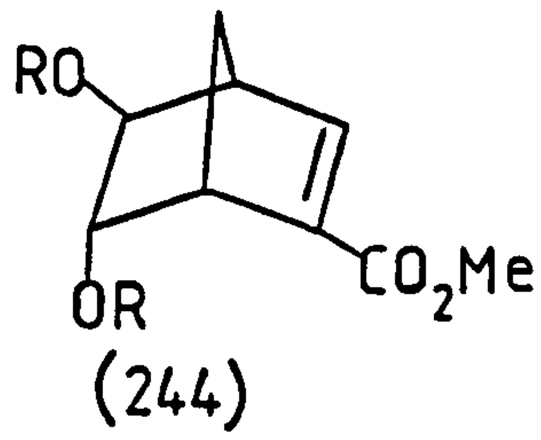


(B1)

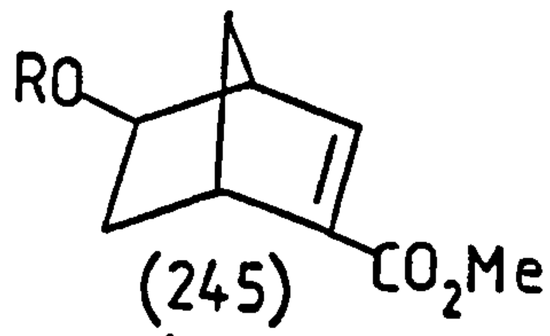
Nucleosides in which all the functionality attached to the furanose ring is β, appear to have received no synthetic study. It was intended to investigate the conversion of the Diels-Alder adduct of cyclopentadiene and maleic anhydride into synthons from which nucleoside analogues could be prepared having this β-stereochemistry on a cyclopentane ring (analogous to the furanose ring of a nucleoside). A reexamination was also to be carried out using the Diels-Alder adduct of furan with fumaryl chloride to see if it could be converted into a suitable synthon for B1.

3.3.0.0. DISCUSSION.

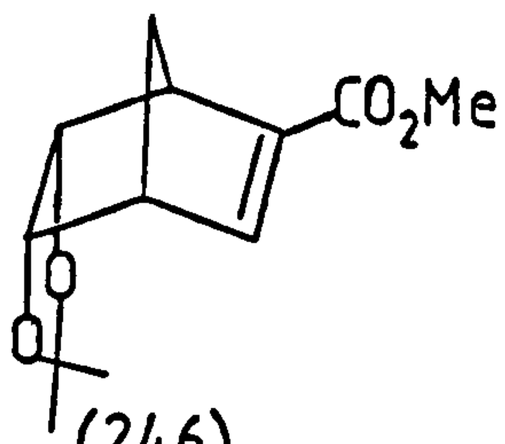
3.3.1.1. Introduction.



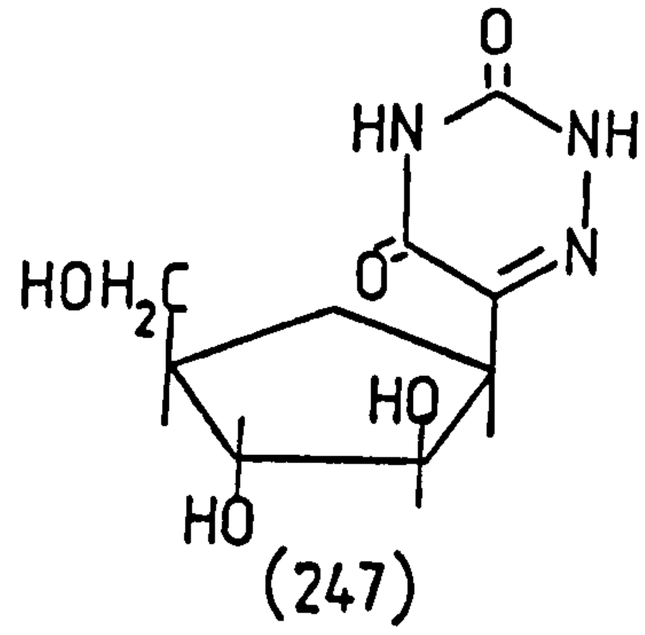
(244)



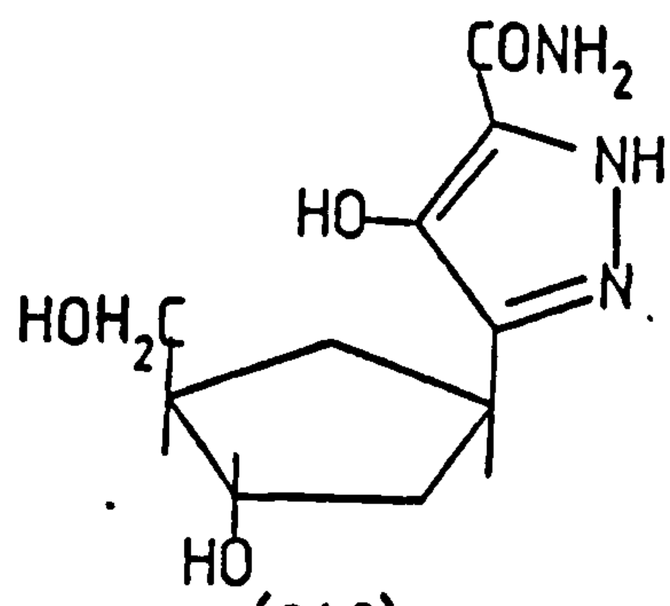
(245)



(246)



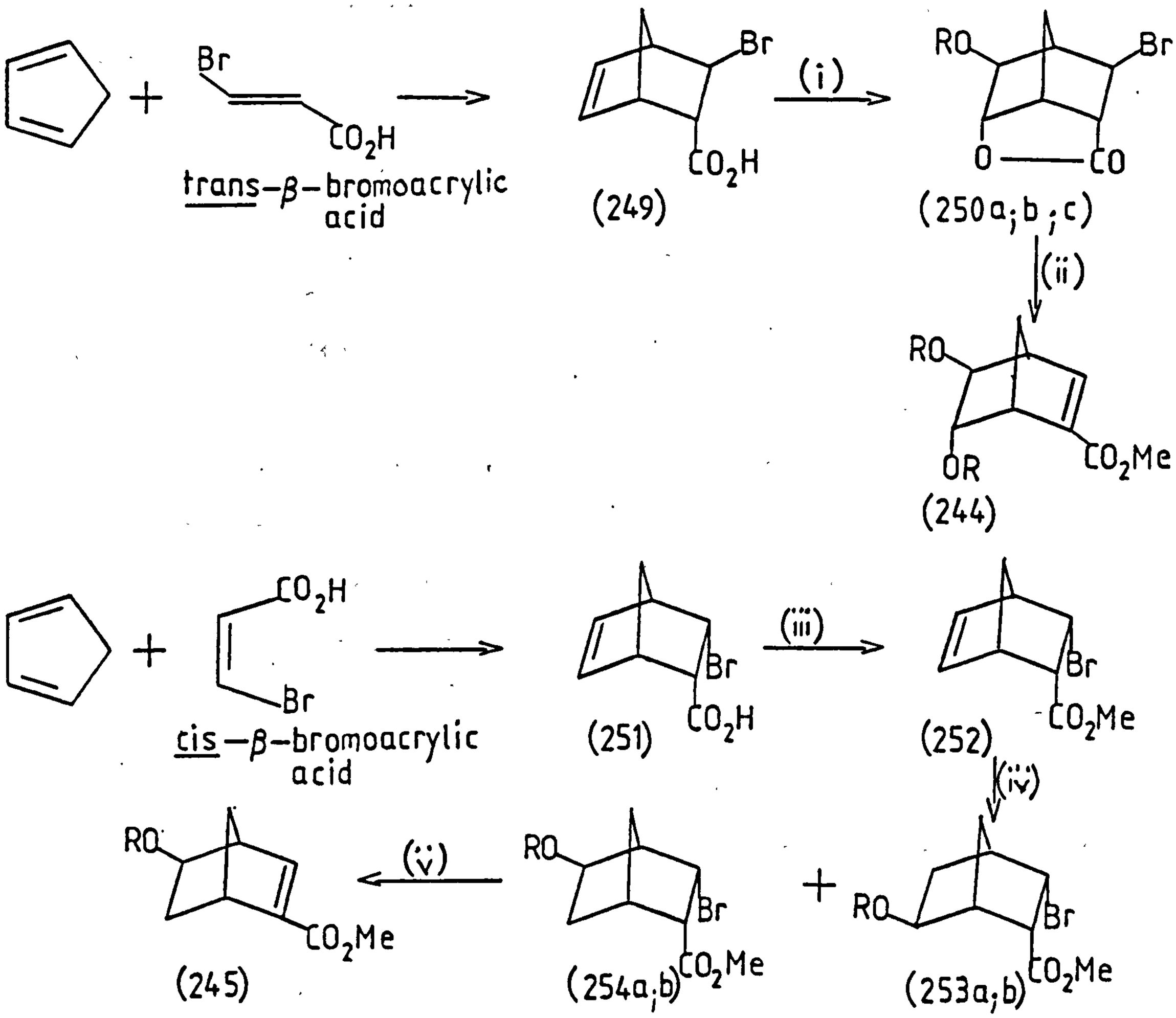
(247)



(248)

Just et al.[177a,b] reported the synthesis of 5-(4'β-hydroxymethyl-2'β-3'α-dihydroxycyclopent-1'β-yl)-6-azauracil (247) and 3(5)-(3'α-hydroxy-4'β-hydroxy-methylcyclopent-1'β-yl)-5(3)-carboxamide-4-hydroxypyrazole (248) from the key intermediates (244); R = Me_3CCO, and (245); R = $COC_6H_4NO_2$-p respectively. These intermediates (244) and (245) were obtained from the Diels-Alder adduct of cyclopentadiene with trans-β and cis-β-bromoacrylic acid as shown in Scheme 23.

Scheme 23



(245) R = $COC_6H_4NO_2$-p (250a) R = H (250b) R = HCO (250c) R = Me_3CCO

(253a, 254a) R = H (253b, 254b) R = $COC_6H_4NO_2$—p

(i) H_2O_2 – HCO_2H (ii) NaOMe (iii) CH_2N_2 (iv) B_2H_6 – H_2O_2

(v) DBU – CH_2Cl_2

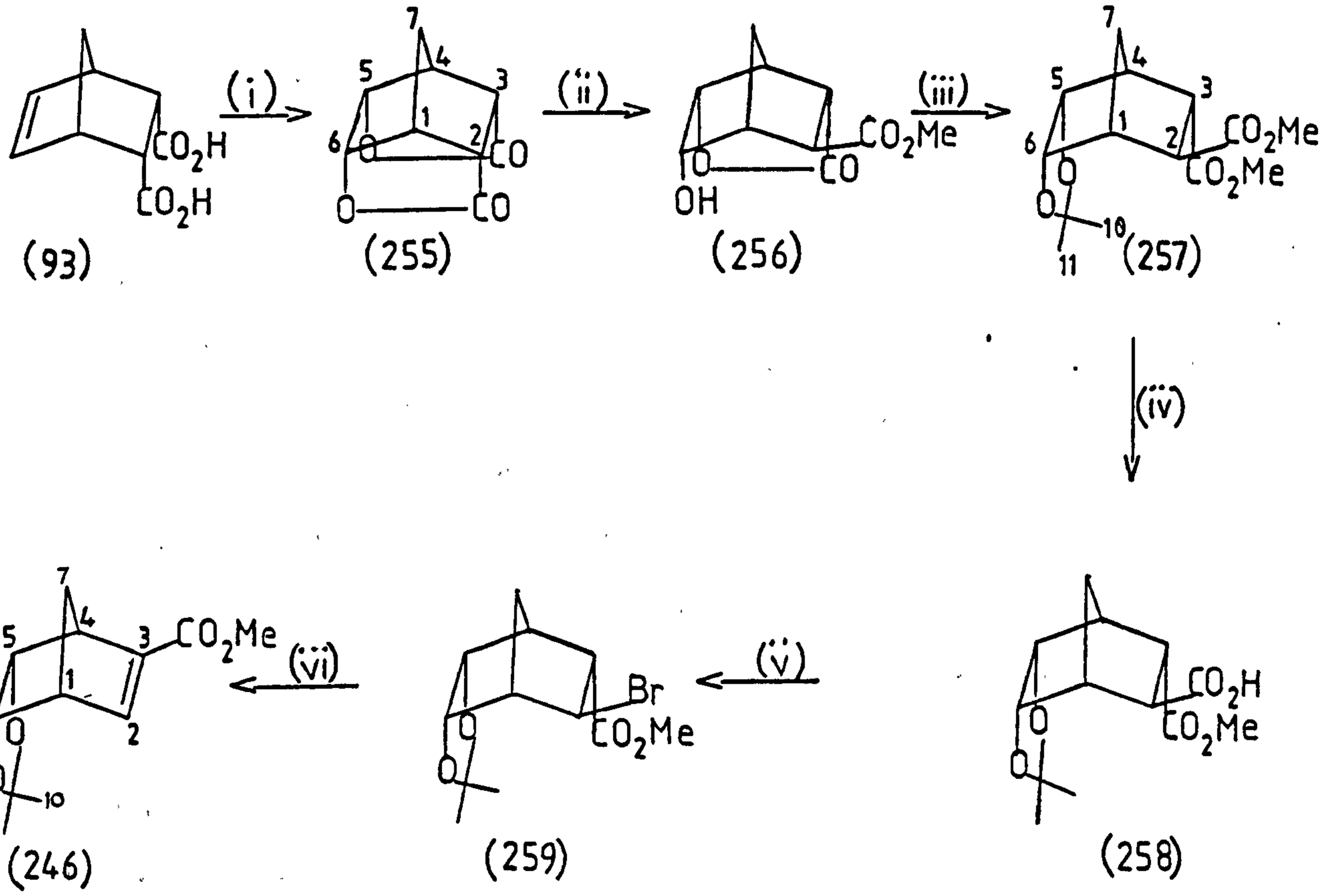
The addition of cyclopentadiene to trans-β-bromoacrylic acid readily gave the adduct (249) which on oxidation with hydrogen peroxide and formic acid afforded (250a) and (250b). Treatment of the hydroxy lactone (250a) with pivaloyl chloride gave the protected pivaloyl compound

(250c). The compound (250c) when subjected to reaction with sodium methoxide, followed by elimination of hydrobromic acid, was converted into intermediate (244). The Diels-Alder addition of cyclopentadiene to cis-β-bromoacrylic acid affords acid (251), which on methylation gave the ester (252). Hydroboration oxidation of the ester (252) afforded a mixture of alcohols (253a) and (254a) in which the hydroxyl function was then protected by treatment with p-nitrobenzoyl chloride to form the p-nitrobenzoates (253b) and (254b). The intermediate (245) was obtained on elimination of hydrobromic acid from (254b) by a reaction with DBU.

In an extension of the above synthetic route it was intended to synthesize the intermediate (246), which is the precursor for an attempt to prepare the C-nucleoside analogue (247), for which the hydroxyl groups at C-2', C-3', C-4', and of the heterocyclic base at C-1', all have β-stereochemistry.

3.3.2.1. Synthesis of 3-Carbomethoxy-5-endo, 6-endo-O-isopropylidenenorborn-2-ene (246).

3.3.2.2. Scheme 24



(i) $Pb(OAc)_4$ — AcOH (ii) NaOMe — MeOH (iii) $MeC(OMe)_2Me$ —HCl

(iv) KOH —t-BuOH (v) HgO $-Br_2$ (vi) $(Et)_3N$ — THF

The Diels-Alder addition of cyclopentadiene to maleic anhydride to give the endo-anhydride adduct (92) is a well established reaction,[96] and the product when hydrolysed with water readily affords the diacid (93) (73%).

The bisγ-lactone (255)[178a-d] (67%) was then obtained by heating a mixture of diacid (93) with lead tetracetate in glacial acetic acid at 100° for 2 h. The lactone (255) exhibited two strong absorptions at 1800 and 1780 cm^{-1} respectively, (>C = O of a γ-lactone) in the infrared . The ^1H nmr spectrum showed a m at δ4.72 (>C<u>H</u>-O-) of H-6-<u>exo</u>, a m at δ3.30 (H-1, H-4), a m at δ3.02 (H-2-<u>exo</u>, H-3-<u>exo</u>) and a m at δ1.80 (H-7<u>anti</u>, H-7<u>syn</u>). The <u>cis</u>-<u>endo</u>-hydroxyl functions at the C-5 and C-6 positions contained in the structure (255), have the required configuration for the intermediate (246). Treatment of the lactone (255) with sodium methoxide in anhydrous methanol at room temperature, resulted in the opening of the lactone function at C-2 - C-6 position to give the hydroxyγ-lactone (256) (83%). The presence of the hydroxyl and ester functions was shown by the ir spectrum which exhibited medium absorption due to these groups at 3350 and 1740 cm^{-1} respectively. The strong absorption at 1770 cm^{-1} (>C = O of a γ-lactone) gave further indication of the presence of a lactone ring at C-3 - C-5 position as in structure (256). The ^1H nmr spectrum showed a t at δ4.50 (H-5-<u>exo</u>) [J(5-<u>exo</u>, 4) = J(5-<u>exo</u>, 6-<u>exo</u>) = 6 Hz] , a q at δ4.0 (H-6-<u>exo</u>) [J(1,6-<u>exo</u>, 1) = 4 Hz] , a s at δ3.65 (-CO_2<u>Me</u>), a brs at δ3.47 (O<u>H</u>), and high field protons at δ3.15-1.42.

Treatment of the hydroxyγ-lactone (256) with 2,2-dimethoxypropane and saturated dry hydrogen chloride in anhydrous methanol results in the opening of the lactone

ring at C-3 - C-5 positions; subsequent protection of the hydroxyls as an isopropylidene function at C-5 - C-6 leads to the product (257). The ir spectrum showed a strong absorption at 1730 cm^{-1} ($\geq C = O$ of methyl ester), and absence of the absorptions at 3530 and 1770 cm^{-1} for (OH) and ($\geq C = O$ of a γ-lactone) found in the starting alcohol (256). The ^1H nmr exhibited a t at δ4.44 ($\geq CH-O-$) integrating for the two protons of H-5exo and H-6exo. Singlets at δ3.72 and δ3.66 were observed corresponding to $-CO_2Me$ at C-2 and C-3 positions respectively. The downfield shift of the $-CO_2Me$ at C-2 in comparison to $-CO_2Me$ in the C-3 position, indicated its exo configuration as is also found in the structure (256) caused by inversion of $-CO_2Me$ by the sodium methoxide during opening of the bisγ-lactone (255). The methyls C-10 and C-11 of isopropylidene function appeared as singlets at δ1.45 and 1.30 respectively.

Partial hydrolysis at the 2-exo-methyl ester function in (257) to the acid (258) was achieved by reaction with potassium hydroxide[142] in a (10:1) mixture of t-butyl alcohol and water at room temperature for 17 h. The acid (258) was obtained in a yield of 75%, and its ir spectrum contained broad absorption of medium intensity at 3200-2500 (COOH), and strong absorptions 1735 and 1710 cm^{-1} consistent with a $\geq C = O$ of an ester and an acid respectively. The ^1H nmr spectrum clearly showed the acid proton as a brs at δ9.22. Singlet at δ3.68 of 3-endo-CO_2Me and the absence of a s at δ3.72 (of 2-exo-CO_2Me in starting 257) is additionally consistent

with the structure (258). The Cristol and Firth modification of the Hunsdiecker reaction[179] for conversion of the carboxylic acids to alkyl halide was applied to the acid (258). Treatment of a well stirred mixture of the acid (258) and red mercuric oxide in carbon tetrachloride (heated at $\sim 95^{o}$), by the dropwise addition of bromine solution in carbon tetrachloride ($\sim$1.5 h) gave the required bromide (259) in a yield of 95%. The bromide (259) showed a strong absorption at 1730 cm^{-1} (>C = O of methyl ester) in the ir spectra. The ^{1}H nmr spectra which appeared as a q at δ4.90 (>C<u>H</u>-Br) of H-2<u>endo</u> [J(2-<u>endo</u>, 3-<u>exo</u>) = 6 and J(2-<u>endo</u>, 7-<u>syn</u>) = 2 Hz], a t at δ4.48 (>C<u>H</u>O-) of H-5<u>exo</u> and H-6<u>exo</u>, and a s at δ3.70 (3-<u>endo</u>-CO_2<u>Me</u>) gave further evidence for the structure (259). The bromide (259) was subjected to a reaction with triethylamine in solvent THF, elimination of the hydrobromic acid as bromide salt of triethylamine took place to give the required 3-carbomethoxy-5-<u>endo</u>, 6-<u>endo</u>-O-isopropylidene-norborn -2-ene (246) in a yield of 77%.

The ir spectrum exhibited a strong absorption at 1730 cm^{-1} indicative of the presence of a methyl ester function. In the ^{1}H nmr spectrum, the olefinic proton of H-2 showed as a d at δ7.04 [J(1,2) = 3 Hz]. A t at δ4.78 (>C<u>H</u>O-) of H-5<u>exo</u> and H-6<u>exo</u>, and a s at δ3.70 of -CO_2<u>Me</u> were consistent with the structure (246). The methyls at C-10 and C-11 of the isopropylidene function in (246) gave rise to singlets at δ1.22 and 1.17 respectively. In comparison the ^{1}H nmr of (257-259) the

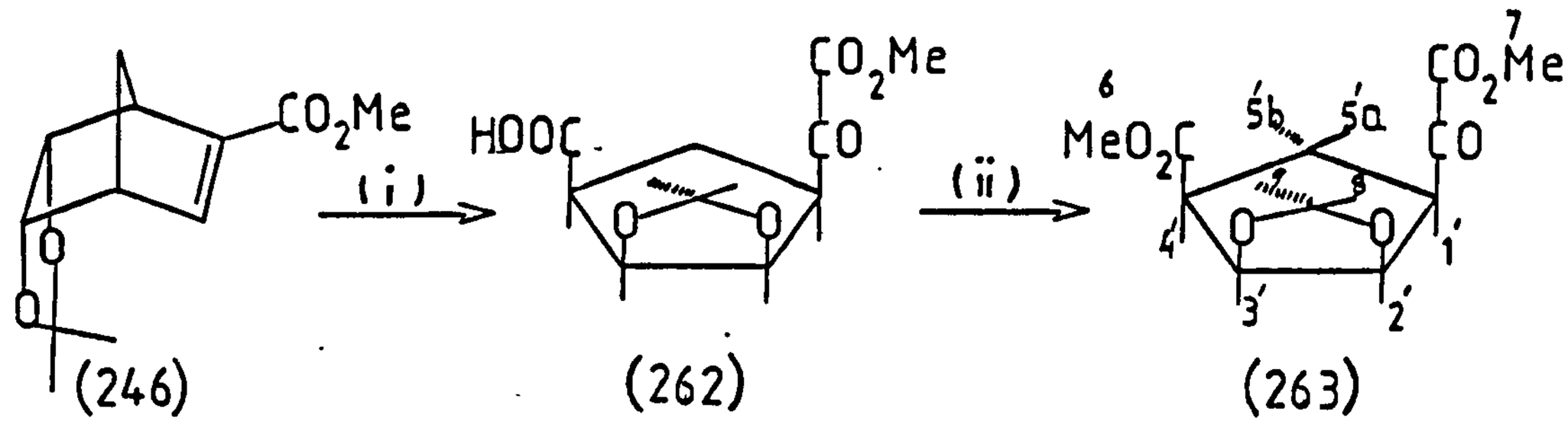
methyls C-10 and C-11 are shifted downfield to about δ1.40 and 1.28. The differences in chemical shifts of the methyl at C-10 and C-11 in (246) and (257-259) is probably due to the deshielding effect by the 3-endo-CO_2Me function in (257) - 259) to the isopropylidene function.

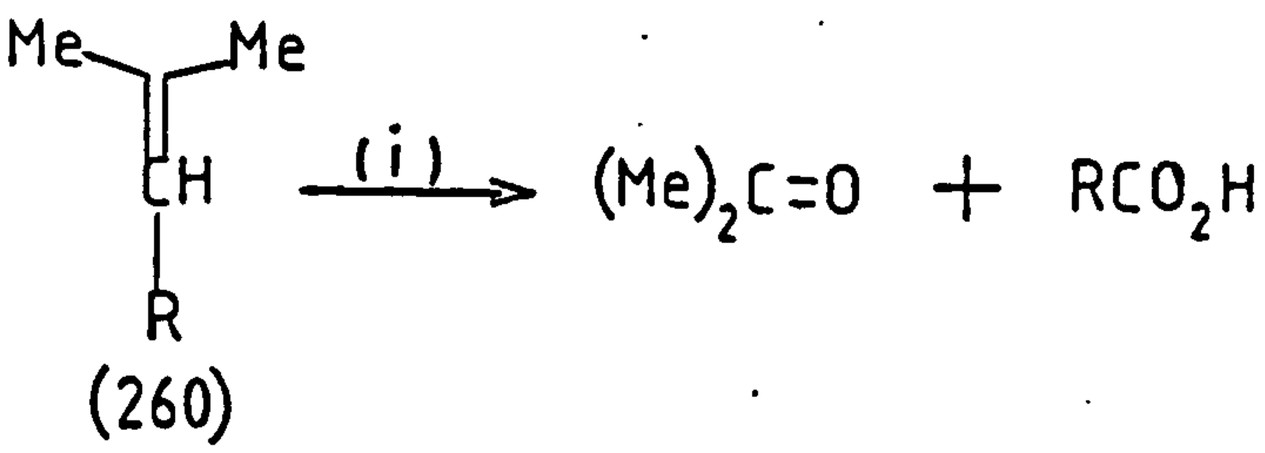
TABLE 21. ^{1}H nmr data for compounds (255→259) and (246).

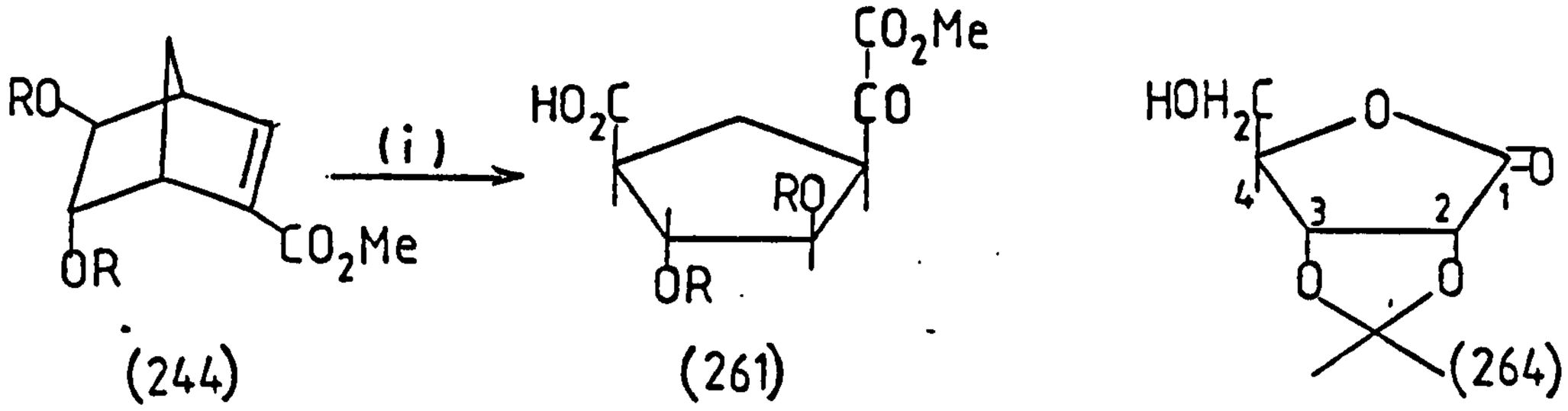
Compound	δ (ppm)												
	1	2-exo	2-endo	3-exo	3-endo	4	5-exo	6-exo	5-endo	6-endo	CH_3-10	CH_3-11	7-anti	7-syn
255	m 3.30	m 3.02		m 3.02		m 3.30	m 4.72						m 1.80	
256	m 2.72	s 3.65	m 3.04	m 3.01		m 3.15	t 4.50	q 4.02		s 3.65			dxt 1.02	brd 1.40
257	m 2.66	s 3.72	dxd 3.54	q 3.23	s 3.66	m 2.97	t 4.44				s 1.45	s 1.30	dxt 1.72	dxq 1.56
258	m 2.75	s 9.22	brd 3.58	q 3.23	s 3.68	m 2.98	t 4.47				s 1.46	s 1.31	brd 1.79	brd 1.57
259	m 2.72		q 4.90	q 3.18	s 3.70	m 2.98	t 4.48				s 1.43	s 1.27	dxt 2.16	dxq 1.72
246	m 3.15	d 7.04		s 3.70		m 3.34	t 4.78				s 1.22	s 1.17	brd 1.52	dxt 1.82

3.3.3.1. Synthesis of Methyl-2-(4'β-Carbomethoxy-2'β-3'β-O-isopropylidenecyclopent-1'β-yl)glyoxylate (263).

3.3.3.2. Scheme 25







(i) $KMnO_4$—$NaIO_4$ (ii) CH_2N_2

Rudloff[180] in his studies into the determination of isopropylidene groups by periodate-permanganate oxidations found that when the isopropylidene group in a compound such as (260) was subjected to oxidation with potassium permanganate and sodium periodate, a quantitative yield of acetone was obtained. Just and Ouellet[177a] recently reported that the keto-acid (261) (40%) could be obtained on oxidative cleavage of the unsaturated ester (244) using the same reagents. The unsaturated ester (246) dissolved in acetone was subjected to reaction with an aqueous solution of

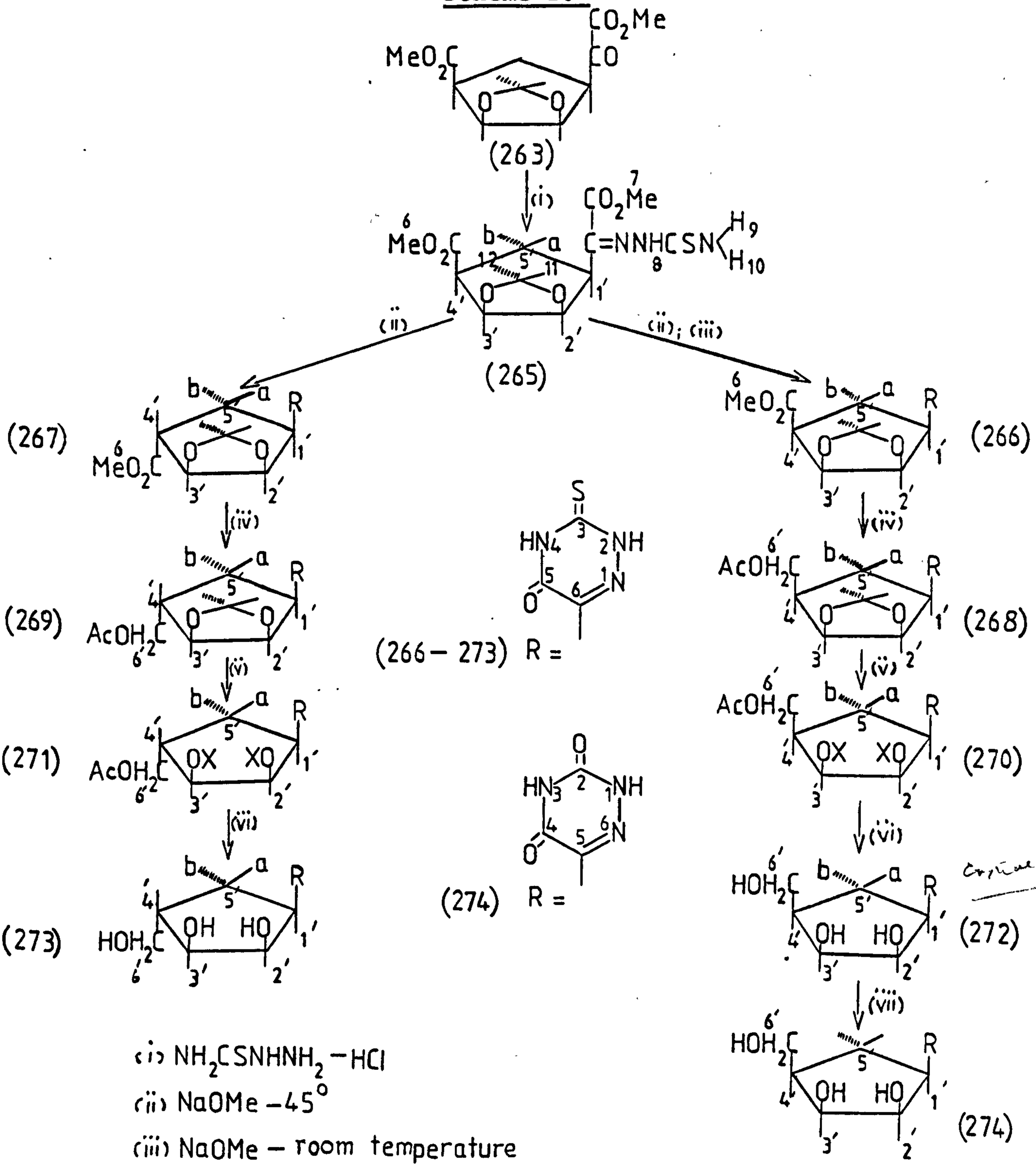
potassium permanganate and sodium periodate; on stirring at room temperature for 16 h the crude product keto-acid (262) resulted and was isolated as the keto-ester (263) (40%) following methylation with diazomethane. In the ir spectrum the keto-ester (263) showed a strong absorption at 1730 cm^{-1} (>C = O of methyl ester). The ^1H nmr contained triplets at δ 5.14 and 4.88 of H-2' and H-3' respectively, [J(1',2') = J(2',3') = J(3',4') = 6 Hz]. Comparison with the published[181] information of 2,3-O-isopropylidene-D-ribono-1-4-lactone (264) which showed J(2,3) = 5.5 Hz and J(3,4) < 0.5 Hz, clearly indicated the coupling constants of 6 Hz to be consistent with the structure (263). Singlets at δ 3.74 and 3.89 of $-CO_2\underline{Me}$ (6) and $-CO_2\underline{Me}$ (7) respectively are consistent with the structure of keto-ester (263). The downfield shift of $-CO_2\underline{Me}$ (7) compared with $-CO_2\underline{Me}$ (6) could be due to the anisotropy of the adjacent carbonyl function, which deshields the protons of the $-CO_2Me$ (7) group.

TABLE 22. ^1H nmr data for compound (263).

δ (ppm)									
H-1'	H-2'	H-3'	H-4'	H-5'a	H-5'b	H-6	H-7	H-8	H-9
dxt	t	t	dxt	q	dxq	s	s	s	s
3.39	5.14	4.88	2.77	2.50	1.89	3.74	3.89	1.24	1.31
J (Hz)									
1'2'	1',5'b	1',5'a	2',3'	3',4'	4',5'b	4',5'a	5'a,5'b		
6	6	10	6	6	5	10	12		

3.3.3.3. The synthesis of 5-(4'β-Hydroxymethyl-2'β-3'β-hydroxylcyclopent-1'β-yl)-6-azauracil (274).

Scheme 26



(i) $NH_2CSNHNH_2 - HCl$

(ii) NaOMe -45°

(iii) NaOMe – room temperature

(iv) $LiAlH_4$ – THF (v) HCO_2H

(vi) NaOH (vii) MeI $-H^+$

(270 — 271) X = CHO

Condensation of the keto-ester (263) with thiosemicarbazide in an aqueous solution of methanol in the presence of a few drops of hydrochloric acid, gave the thiosemicarbazone (265) (80%). The ir spectrum exhibited a medium absorption at 3300 and 3200 cm^{-1} (NH) and a strong absorption at 1725 cm^{-1} ($\geq C = O$ of the methyl ester). The ^1H nmr spectrum showed broad singlets at δ 12.24 and 7.0 respectively integrating for the one and two protons attached to C-8 and C-9. A q at δ 4.80, singlets at δ 3.90, 3.75, 1.31 and 1.25 of (H-2' and H-3'), $-CO_2\underline{Me}$ (7), $-CO_2\underline{Me}$ (6), $-\underline{CH_3}$ (12) and $-\underline{CH_3}$ (11) respectively are also contained in the ^1H nmr spectrum. During the first attempt at cyclisation of the thiosemicarbazone (265) with 3 moles excess of sodium methoxide at 45° for 45 mins afforded a mixture of 1,2,4-triazines (266) and (267) isolated in a 1.1:1 molar ratio. The formation of 1,2,4-triazine (267) is most likely due to the isomerisation of the $-CO_2Me$ at C-4' (266) due to the presence of excess sodium methoxide. When the same mole proportion of sodium methoxide was used at room temperature and following the reaction with t.l.c., a complete disappearance of starting thiosemicarbazone (265) was observed after 30 mins. The product 1,2,4-triazine (266) was the sole product obtained in a yield of 78%. In the ir spectrum both of the 1,2,4-triazines (266) and (267) showed a medium and a strong absorption at 3400 and 1720 cm^{-1} of (NH) and ($\geq C = O$ of the methyl ester and heterocyclic triazine rings) respectively. The ^1H nmr of 1,2,4-triazines (266) showed triplets at δ5.06 and 4.96 of H-2' and H-3' [J(1',2') = J(2',3') = J(3',4') = 5.2 Hz] while in the case

of (267), the protons H-2' and H-3' gave rise to an overlapping quintet centred at δ4.98. The overlapping of H-2' and H-3' in (267) is probably due to a downfield shift of H-3', because of its close proximity to the 4'α-CO_2Me group which gives more deshielding than the 4'β-CO_2Me group of (266). The presence of cyclic 1,2,4-triazines in both compounds (266) and (267) were shown from the uv spectrum, which exhibited a λmax at 271 nm ($\log\varepsilon$ 4.30). The uv data was consistent with the published uv information[177a] of 6-(4'β-carbomethoxy-2'β,3'α-dipivaloyloxycyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one which showed λmax (CH_3OH) at 272 nm ($\log\varepsilon$ 4.19).

Reduction of the 4'β- and 4'α- methyl ester functions of 1,2,4-triazines (266) and (267) with lithium aluminum hydride in tetrahydrofuran afforded the corresponding alcohols, which when treated with acetic anhydride in pyridine gave the acetates (268) and (269) in yields of 78% and 73% respectively. The acetates (268) and (269) exhibited medium and strong absorptions at 3400 and 1730 cm^{-1} of (-NH) and (≥C = O of acetoxy function and heterocyclic 1,2,4-triazines ring) respectively. The presence of ≥C = O and ≥C = N functions in the heterocyclic 1,2,4-triazines (268) and (269) was further indicated from the uv spectra which exhibited a respective λmax (CH_3OH) at 271 nm ($\log\varepsilon$ 4.02) and 271 nm ($\log\varepsilon$ 4.17) similar to the starting (266) and (267). The ^1H nmr spectrum showed brs at δ12.2 and 11.2 of N-H in (268) and (269)

respectively. A t at δ5.04 [J(1',2') = J(2',3') = 6 Hz] of H-2', a t at δ4.73 [J(2',3') = J(3',4') = 6 Hz] of H-3' and a d at δ2.01 of $\underline{CH_3}CO_2$- are consistent with the structure (268). In the case of (269), the spectrum showed a t at δ5.04 of H-2' [J(1',2') = J(2',3') = 5 Hz], a d at δ4.59 of H-3' [J(2',3') = 5 Hz], a d at δ4.0 [J(4',6') = 7 Hz] of 4'α-$\underline{CH_2}$-OAc with a sharp singlet at δ2.04 of $\underline{CH_3}$-$\underline{CO_2}$-. The H-3' proton in (269) which exhibited a d at δ4.59 was a strong indication for the 4'α-$\underline{CH_2}$-OAc position, because the observed trans-coupling constants of J(3',4') ≈ 0 was consistent with the published information[181] for 2,3-O-isopropylidene-D-ribono-1,4-lactone (264) in which J(3,4) < 0.5 Hz. The high field shift of 4'α-CH_2-OAc which resonated at δ4.0 compared with δ4.20 for 4'β-$\underline{CH_2}$-OAc in (268) is also consistent with the structure (269).

The hydroxyl-protecting isopropylidene functions in (268) and (269) were removed by stirring at room temperature with 98% formic acid[182] to afford (270) and (271) respectively. The shorter reaction time for (269) (17 h) than for its isomer (268) (48 h) is also consistent with the 4'α-CH_2-OAc position in (269) so that the isopropylidene function at C-2' - C-3' are less hindered to the attack of formic acid than is the more crowded system in (268) because of the presence of 4'β-CH_2-OAc.

The absence of singlets at δ1.22 and 1.28 due to the isopropylidene functions (in starting 268 and 269),

was noted in the ^1H nmr spectrum of (270) and (271) which showed a new singlet at δ8.10 of H-COO- at C-2' - C-3' integrating for two protons. Treatment of the compounds (270) and (271) with aqueous sodium hydroxide afforded the triols (272) and (273) respectively. The triols (272) and (273) exhibited medium and strong absorptions at 3400 (OH and NH) and 1680 cm^{-1} (>C = O of heterocyclic 1,2,4-triazines ring). The uv spectra of (272) and (273) were similar to those of the earlier compounds (266-271) and showed a λmax (CH_3OH) at 271 nm ($\log\varepsilon$ 4.06), and at 271 nm ($\log\varepsilon$ 4.25) respectively. The ^1H nmr spectrum of (272) and (273) showed triplets at δ5.11 and 5.25 of H-2', quartets at δ4.73 and 4.60 of H-3', a d at δ4.27, a dxq at δ4.24 of H-6', and high field protons at δ3.90 - 2.10 respectively. In the mass spectral data, the triols (272) gave a molecular ion m/e ($M^{+\cdot}$) while the triols (273) exhibited a high abundance peak at 241 corresponding to ($M^{+\cdot} - H_2O$) which further supports the formation of (272) and (273).

In an attempt to synthesize the 6-azauracil (274) by replacing the sulfur atom with an oxygen atom in (272), the triol (272) was first subjected to a reaction with methyl iodide in water and heated at 55° for 6 h. Removal of the excess methyl iodide followed by subsequent acid hydrolysis with Dowex 50W-X8(H^+)[177a] afforded a semi solid product. The product showed a λmax (CH_3OH) 267 nm ($\log\varepsilon$ 3.68) comparable with 5-(4'β-hydroxymethyl-2'β, 3'α-dihydroxycyclopent-1'β-yl)-6-azauracil (247)[177a] for which λmax (H_2O) 265 nm ($\log\varepsilon$ 3.75).

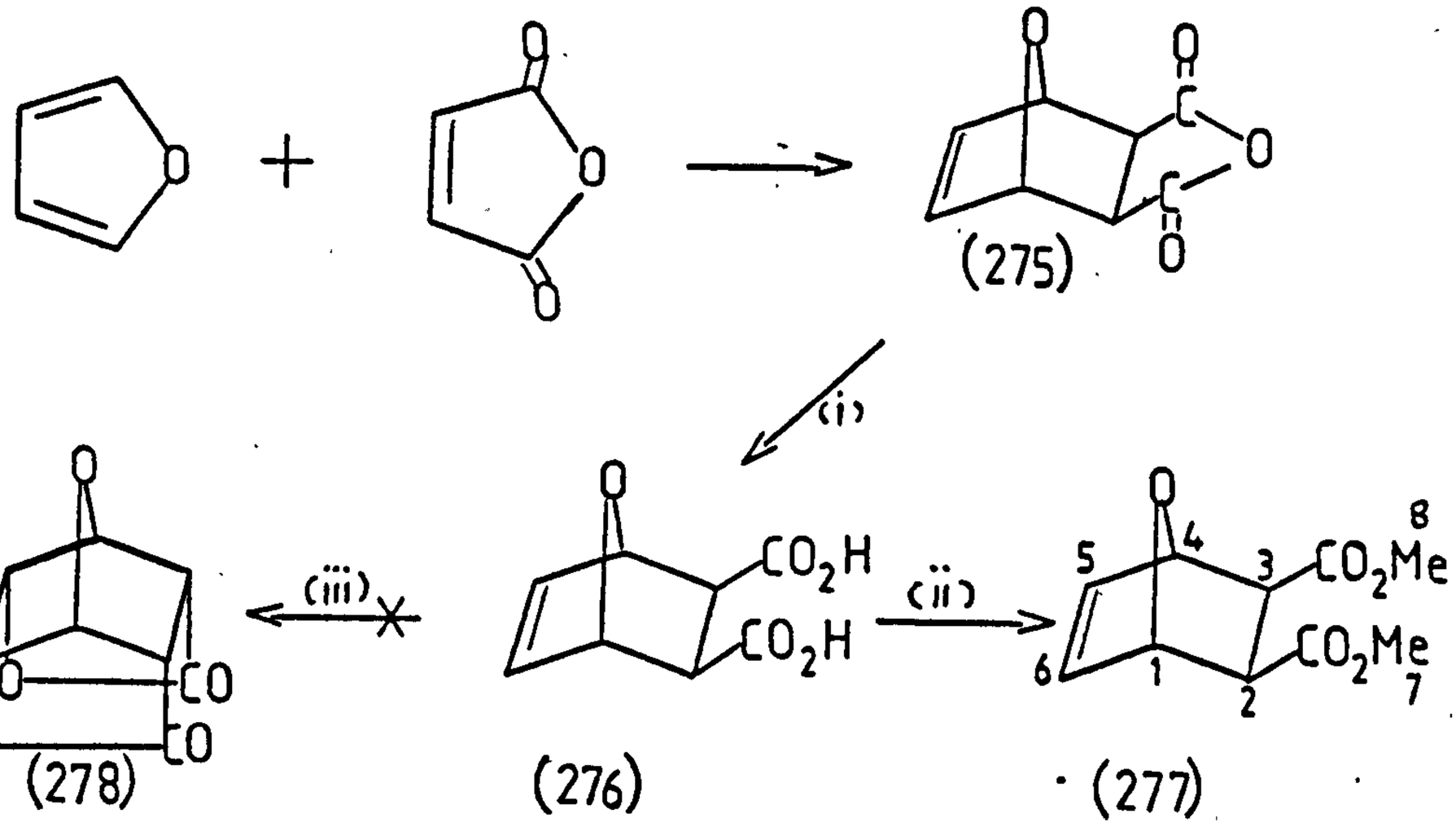
Unfortunately the mass spectrum contained only a fragmentation at 215, 155, 145, 127 and 123 respectively, none of which correspond to the required m/e 243 ($M^{+\cdot}$) or at least 225 ($M^{+\cdot} - H_2O$). In a second attempt the triol (272) was subjected to the same reaction with methyl iodide and heated at 55° for 6 h. After removing the excess methyl iodide the resultant solution was further heated at 100° for 1 h and then neutralised with Dowex 1-X8 (Formate)[160] to afford a product the uv spectrum of which showed a λmax (CH_3OH) 266 nm (logε 3.70), similar to the uv spectrum of the 6-azauracil (247). The mass spectrum showed a fragmentation at 225, 224, 196 and 170 respectively. This uv and mass spectral evidence suggests that this product contains the required 6-azauracil (274); the fragmentation at 225 and 196 in the mass spectrum might correspond to ($M^{+\cdot} - H_2O$) and ($M^{+\cdot} - H_2O - CO$) respectively in (274). The final stage in the synthesis of (274) is similar to the procedure used by Just and Ouellet[177a] in the final stage of their synthesis of 5-(4'β-hydroxymethyl-2'β,3'α-dihydroxycyclopent-1'β-yl)-6-azauracil (247). The only evidence they have for the structure of the product is just the uv spectrum. In our synthesis we have provided both a satisfactory uv spectrum and consistant mass spectral data.

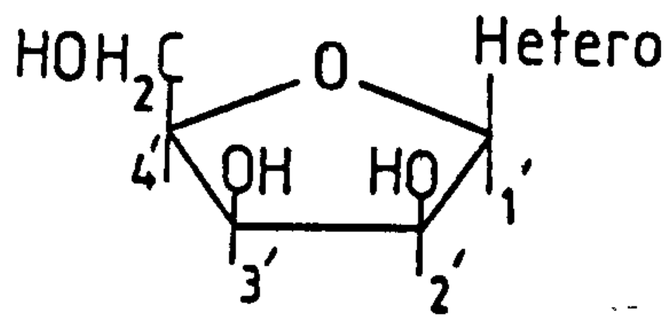
TABLE 23. ^{1}H nmr data for compounds (265-273).

Compound	δ (ppm)												
	H-1'	H-2'	H-3'	H-4'	H-5'a	H-5'b	H-6'a	H-6'b	CO_2Me(6)	CO_2Me(7)	$(CH_3)_2C$-	CH_3COO-	HCOO-
265	m 3.10	q 4.80		m 2.80	q 2.47	sextet 1.88			s 3.75	s 3.90	s 1.31 s 1.25		
266	sextet 3.24	t 5.06	t 4.96	sextet 3.02	q 2.50	sextet 1.84			s 3.67		s 1.26 s 1.21		
267	m 3.45	quintet 4.98		m 3.45	q 2.80	dxq 2.40			s 3.68		s 1.29 s 1.23		
268	quintet 3.25	t 5.04	t 4.73	m 2.20		m 1.80	d 4.20				s 1.28 s 1.22	s 2.01	
269	quintet 3.36	t 5.02	d 4.59	m 2.50		m 1.80	d 4.0				s 1.28 s 1.23	s 2.04	
270	m 3.70	m 5.70		m 2.30	m 2.80	m 2.30	d 4.20					s 2.05	s 8.10
271	m 3.8	t 5.70	q 5.30		m 2.90		d 4.20					s 2.08	s 8.10
272	dxq 3.74	t 5.11	q 4.73	m 2.60	sex-tet 2.95	sex-tet 2.10	d 4.27						
273	sextet 3.90	t 5.25	q 4.60	dxq 2.95	sex-tet 3.30	dxq 2.15	dxq 4.24						

3.3.4.1. Approaches to the synthesis of 2-Carbomethoxy-5-endo,6-endo-O-isopropylidene-7-exo-bicyclo [2.2.1.] hept-2-ene (289).

Scheme 27A

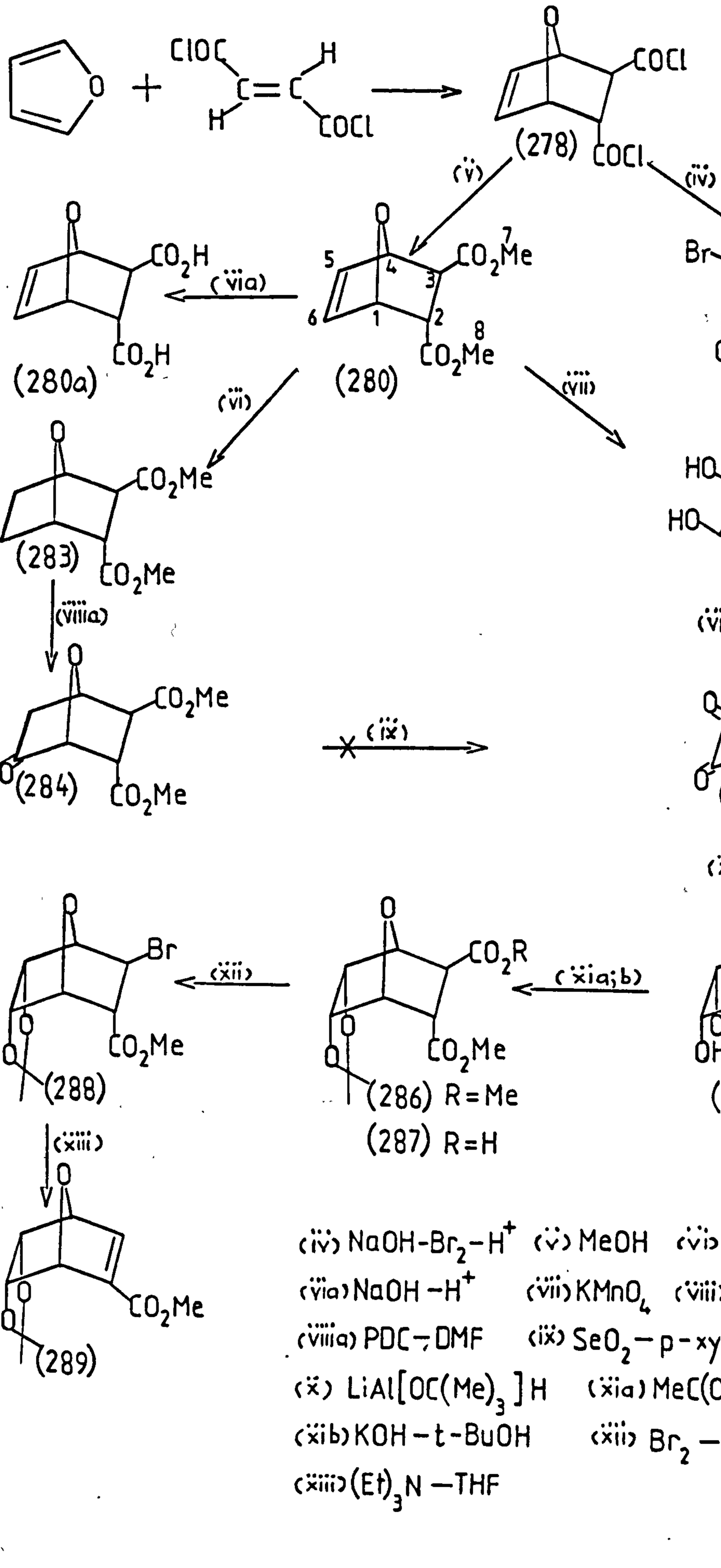




(B1)

(i) H_2O (ii) CH_2N_2 (iii) $Pb(OAc)_4$ — AcOH

Scheme 27B



(iv) $NaOH-Br_2-H^+$ (v) MeOH (vi) $B_2H_6-NaOH-H_2O_2$

(via) $NaOH-H^+$ (vii) $KMnO_4$ (viii) PDC-DMF ; $CrO_3-H_2SO_4$

(viiia) PDC-DMF (ix) SeO_2 – p-xylene

(x) $LiAl[OC(Me)_3]H$ (xia) $MeC(OMe)_2Me$ –TsOH

(xib) KOH – t-BuOH (xii) Br_2 – HgO

(xiii) $(Et)_3N$ – THF

In an attempt to prepare C-nucleosides such as B-1, for which the stereochemistry of the hydroxyl groups at C-1', C-2', C-3', C-4' and of the heterocyclic base at C-1' are all β, the key intermediate required is the unsaturated ester (289) analogous to the unsaturated ester (246) prepared earlier.

The Diels-Alder addition of furan to maleic anhydride affords the exo-anhydride (275)[183] which was obtained in 41% yield. Hydrolysis of the anhydride (275) with water at 60°,[184] gave the exo-acid (276) in 81% yield, and on methylation with diazomethane the exo-ester (277)[184,187] was obtained in 72% yield. The exo-ester (277) exhibited a strong absorption at 1735 cm^{-1} (>C = O of methyl ester) in the infrared. The ^1H nmr showed a m at δ6.45 for olefinic protons H-5 and H-6, a brs at δ5.23 of H-1 and H-4, a s at δ3.68 of $-CO_2\underline{Me}$, and a s at δ2.82 of H-2endo and H-3endo. A s at δ2.82 showed the protons of H-2endo and H-3endo are equivalent and do not douple with bridgehead protons 1 or 4 consistent with the exo-stereochemistry of the methyl ester functions at C-2 - C-3 positions in (277), which are also contained in (275) and (276). Because of the exo-stereochemistry of the carboxylic acid functions in (276) oxidation with lead tetracetate [as for the acid 93 in Scheme 24] could not form the bisγ-lactone (276a) [Scheme 27A].

Scheme 27B shows in outline how it was thought the required intermediate (289) might be obtained. Addition of fumaryl chloride[185] to furan afforded the unisolated adduct (278) which was readily converted to

the bromoacidγ-lactone (279a R = H)[185,186] in a yield of 37%. Easier identification was achieved in ^{1}H nmr by conversion to the bromoesterγ-lactone (279b R = Me) on methylation with methanol in the presence of sulphuric acid. The ^{1}H nmr spectrum of (279b) showed a t at δ5.50 of H-1 with J(1,6-exo) = J(1,2-exo) = 6 Hz, a brs at δ5.13 of H-4, a d at δ5.0 (>C<u>H</u>-O-) of H-6exo with J(1,6-exo) = 6 Hz, a s at δ3.97 (C<u>H</u>-Br) of H-5endo, a s at δ3.80 of -CO_2<u>Me</u>, a brd at δ3.40 of H-2exo and a brs at δ3.12 of H-3endo. The carbonyls of a γ-lactone and methyl ester were shown as strong absorptions at 1800 and 1740 cm^{-1} respectively in the infrared . The observed reversibility of the adduct (278) to starting materials furan and fumaryl chloride on heating made it not possible for (278) to be isolated and purified by distillation. Treatment of the crude reaction product with methanol gave the trans-methyl ester (280) in a yield of 57%.

The trans-methyl ester (280) showed a strong absorption at 1740 (>C = O of methyl ester) in the infra red. The ^{1}H nmr spectrum contained a m at δ6.40 (olefinic protons) of H-5 and H-6, a m at δ5.22 of H-1 and H-4, a s at δ3.73 of -CO_2<u>Me</u> (7), a s at δ3.67 of -CO_2Me (8), a t at δ3.60 of H-2exo with J(1,2-exo) = J(2-exo, 3-endo) = 5 Hz, and a d at δ2.84 of H-3endo. The ^{1}H nmr spectrum of (280) was consistent with the spectrum shown by Eggelte et al.,[187] who obtained the trans-ester (280) by isomerisation of the cis-exo ester (277) with NaOMe/MeOH. Permanganate oxidation[188] of the ester (280) gave the diol (281) in a yield of 52%. In the infra red the diol

(281) exhibited a medium and a strong absorption at 3400 and 1740 cm^{-1} of -OH and $\geq C = O$ of methyl ester function respectively. The ^1H nmr spectrum contained a s at δ4.65 of H-4, a d at δ4.50 of H-1 with J(1,2-exo) = 6 Hz, a brs at δ3.90 ($\geq$CH-O-) of H-5endo and H-6endo, and high field protons at δ3.70 - 3.0. Unfortunately several attempts made to oxidise the diol (281) to the diketone (282) either by using pyridinium dichromate or chromic acid were unsuccessful and led only to the unchanged diol (281) contaminated with unidentified product. In an attempt to obtain the diketone (282), the alternative routes (vi), (viiia) and (x) in Scheme 27B were examined. Hydroboration oxidation[189] of the trans-ester (280) afforded the exo-alcohol (283) in 79% yield. In the infrared the alcohol (283) exhibited a medium and a strong absorption at 3400 and 1740 cm^{-1} of -OH and $\geq C = O$ of methyl ester respectively. The ^1H nmr showed a d at δ4.80 of H-1 with J(1,2-exo) = 6 Hz, a brd at δ4.56 of H-4 with J)4,5-exo) = 5 Hz, a brt at δ3.95 ($\geq$CH-O-) of H-6endo with J(5-exo, 6-endo) = J(5-endo, 6-endo) = 5 Hz and high field protons at δ3.70 - 1.70 with a m centred at δ1.90 of H-5exo and H-5-endo, which were consistent with the structure (283).

Oxidation of the alcohol (283) with pyridinium dichromate in DMF gave the ketone (284) in a yield of 61%. The ketone (284) exhibited a strong absorption at 1740 cm^{-1} for the $\geq C = O$ of the methyl ester and ketone functions. In the ^1H nmr was observed a brd at δ5.20 of H-1 with J(1,2-exo) = 6 Hz, a brd at δ4.60 of H-4 with

J(4,5-exo) = 6 Hz, a s at δ3.72 of $-CO_2Me$ (6) and (7), a t at δ3.62 of H-2exo with J(1,2-exo) = J(2-exo, 3-endo) = 5 Hz, and high field protons at δ3.30 - 2.20. Oxidation of the ketone (284) to diketone (282) with selenium dioxide[190] in p-xylene at 150° for 4 h, 8 h, 16 h and 24 h only led to unchanged ketone (283).

If the diketone (282) could be obtained, reduction by lithium aluminum tri-t-butoxyhydride[191] would afford predominantly the endo-diol (285) from which on treatment with 2,2-dimethoxypropane in the presence of p-toluene-sulphonic acid, the protected ester (286) could be obtained. Partial hydrolysis of the trans-ester (286) with potassium hydroxide in t-butanol, such as can be carried out on the related ester (257) (Scheme 24) might lead to the acid (287) which on treatment with bromine and mercuric oxide should be convertible to the bromide (288). Elimination of the hydrobromic acid by heating (288) with triethylamine should readily proceed to give the required intermediate (289). Because no successful route to the diketone (282) could be devised, the final steps (x) - (xiii) required to afford synthon (289) could not be carried out.

TABLE 24. ^{1}H nmr data for compounds (277) - (284)

Compound	δ (ppm)												
	H-1	H-2exo	H-2endo	H-3exo	H-3endo	H-4	H-5exo	H-6exo	H-5endo	H-6endo	$-CO_2Me$(7)	$-CO_2Me$(8)	OH
277	brs 5.23		brs 2.82		brs 2.82	brs 5.23	m 6.15				s 3.68		
279a	t 5.60	q 3.23			d 3.42	brs 5.09		brd 5.0	s 4.35				
279b	t 5.50	brd 3.40			brs 3.12	brs 5.13		d 5.0	brs 3.97			s 3.80	
280	m 5.22	t 3.60			d 2.84	m 5.22	m 6.40				s 3.73	s 3.67	
281	d 4.50	t 3.45			d 3.0	s 4.65			brs 3.90		s 3.70		brs 3.60
283	d 4.80	brt 3.40			brd 2.90	d 4.56	m 1.90		m 1.90	brt 3.95	s 3.70		brs 3.40
284	d 5.20	t 3.62			d 3.30	d 4.60	m 2.35		m 2.35		s 3.72		

4.0.0.0. CHAPTER 4. EXPERIMENTAL

4.1.1.0. General Techniques

4.1.1.1. Infrared

Infrared spectra were recorded on a Perkin Elmer 257 grating infrared spectrophotometer. Samples were prepared as 1-5% solutions in chloroform or as Nujol mulls.

4.1.1.2. Ultraviolet

Ultraviolet spectra were recorded on a S.P.800 Ultraviolet Spectrophotometer (Unicam) fitted with 1 cm thick square silica cells containing Analar methanol solution, (unless otherwise stated) prepared by dissolving the sample (1 mg for M.W 200) in 100 ml.

4.1.1.3. N.M.R.

N.M.R. spectra were recorded on a Perkin Elmer K12B for 60 MHz, Bruker HFX 90 for 90 MHz and Bruker WM 250 for 250 MHz. Unless stated otherwise samples (10-30 mg) were dissolved in deuterochloroform (0.5 ml) containing tetramethylsilane as internal standard. Chemical shifts δ are given in p.p.m. downfield from the reference tetramethylsilane (TMS).

4.1.1.4. Thin layer chromatography (t.l.c.)

For analytical purposes plastic plates (20 x 20 cm) coated with Kieselgel 60F254 in 0.2 mm thickness were used.

4.1.1.5. Preparative layer chromotography (p.l.c.)

Preparative plates were made by coating 20 x 20 cm glass plates to 0.1 cm thickness using a slurry of Kieselgel GF254 (Type 60) prepared as follows: Batches of 6 plates were coated with a slurry of Kieselgel (120 g) and water (220 ml) then dried at 110° for 16 h. The plates were pre-run with methanol and dried at 110° for 6 h.

4.1.1.6. Column chromatography

Silica gel (Merck H Type 60; 40 g/1 g of mixture to be separated) was used as adsorbent and unless otherwise stated light petroleum (b.p. 60-80°)/ethyl acetate mixtures as eluent.

4.1.1.7. Melting points

Melting points were recorded using a hot-stage microscope (Reichert).

4.1.1.8. Gas liquid chromatography (g.l.c.)

Gas liquid chromatographic analysis was carried out using a Perkin Elmer F11 F.I.D. gas chromatography fitted with (unless stated otherwise) 2mx 1/8" stainless steel columns packed with Carbowax 20M on Chromosorb W (80-100 mesh) and using nitrogen as carrier gas.

4.1.1.9. Mass spectra

The spectra were recorded on an AF1 MS30 double focussing mass spectrometer.

4.1.1.10. Purification of solvents

Methanol (b.p. 64.5-65.5°) was purified by the procedure of Vogel;[111] diethyl ether was dried over sodium wire or by refluxing over lithium aluminum hydride for 3 h and then distilled (b.p. 34-35°); tetrahydrofuran (THF) was dried by refluxing over lithium aluminum hydride (0.2 g per 100 ml THF) for 3 h and then distilled (b.p. 65-66); acetonitrile (b.p. 81-82°), p-dioxane (b.p. 100-102°), and dimethyl sulphoxide (DMSO) (b.p. 189-192°) were dried by refluxing over powdered calcium hydride (1.0 g) per 100 ml of solvent) for 2 h prior to distillation immediately prior to use. Cyclopentodiene was obtained by cracking dicyclopentadiene in a distillation flask fitted with a fractionating column. The distillate of cyclopentadiene (b.p. 40-42°) was collected immediately prior to use.

4.1.1.11 Methylation of organic acids with diazomethane

N-Nitrosomethylurea (1.04 g, 10 mmol), prepared by the method of Vogel[111] was slowly added to the ether layer (50 ml) above a (50%) solution of potassium hydroxide (15 ml) cooled at 0°. After about 1 h, the solid of N-Nitrosomethylurea had dissolved and the layers had become yellow in colour. The ethereal layer containing diazomethane was separated and slowly added to a solution of organic acid (67 mmol) in ether. After 1 h, when the solution is still yellow excess diazomethane was removed by blowing a stream of air over the surface of the ether solution until the yellow colour disappeared. The solvent was removed under reduced pressure to give the product.

4.1.1.12. Abbreviations

4.1.1.12a Solvents and Chemical Reagents

DMSO - Dimethylsulphoxide

Et_2O - Diethyl ether

DMF - Dimethylformamide

THF - Tetrahydrofuran

Py - Pyridine

AcOH - Acetic acid

Ac_2O - Acetic anhydride

PDC - Pyridiniumdichromate

TsCl - Tosyl chloride

4.1.1.12b ^1H and ^{13}C nmr spectrum

s - singlet

d - doublet

m - multiplet

br - broad

q - quartet

t - triplet

4.1.1.12c IR spectrum

w - weak

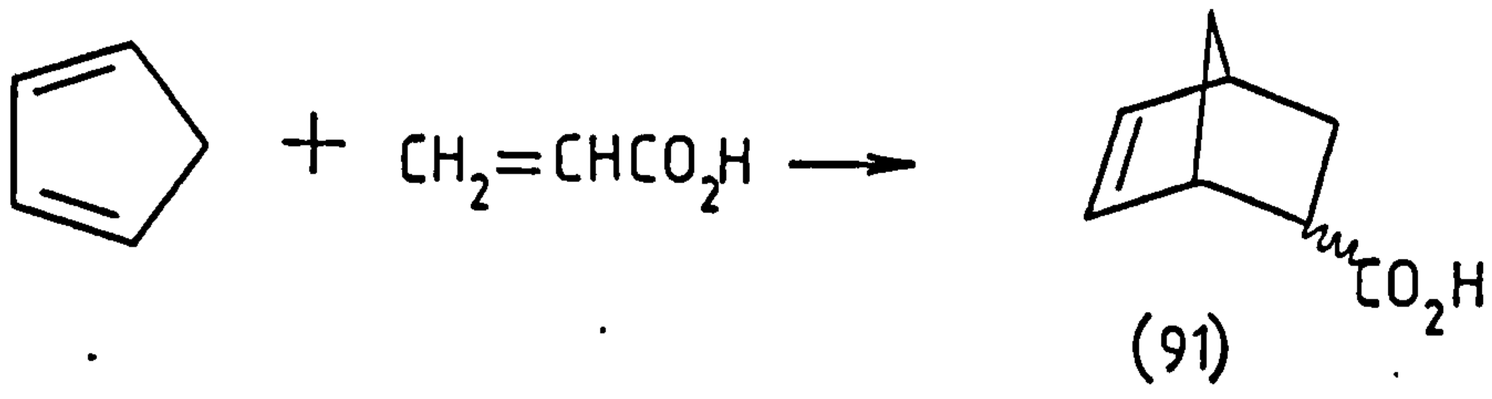
m - medium

s - strong

br - broad

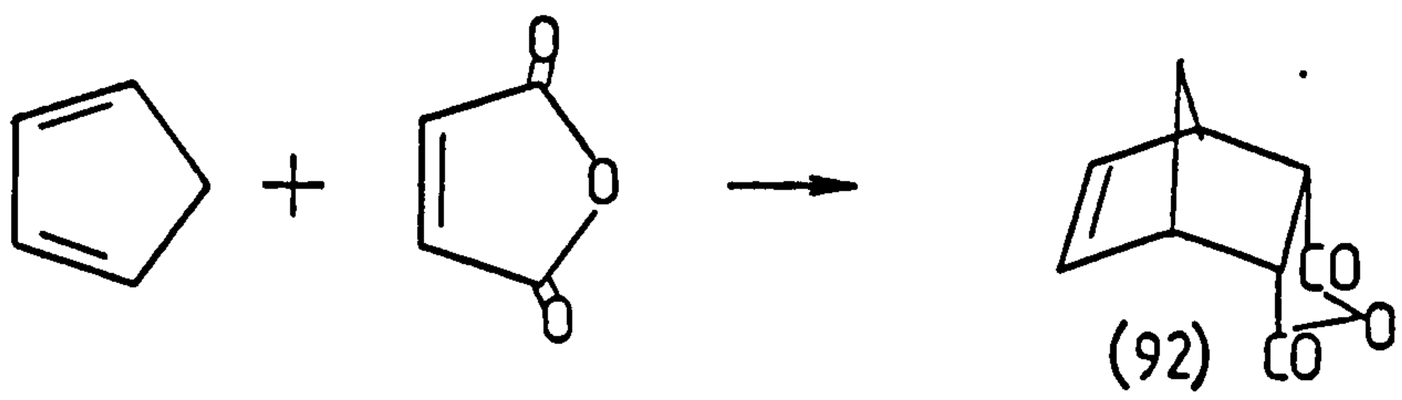
4.2.2.0. Synthesis of starting materials

4.2.2.1. Norborn-5-en-2-ylcarboxylic acid (91).—



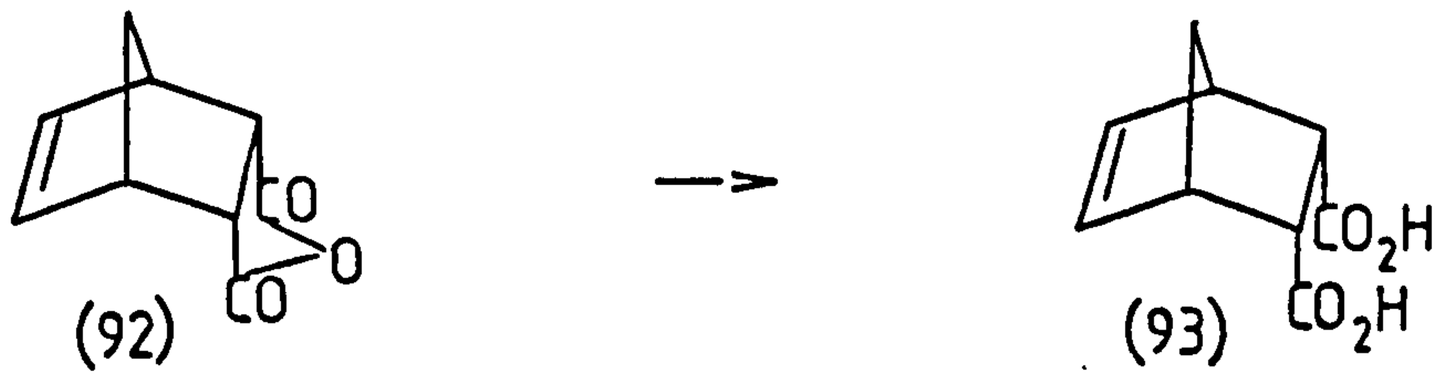
The acid (91) (a mixture of exo and endo isomers) was prepared from cyclopentadiene (8.50 g, 0.13 mole) and acrylic acid (8.50 g, 0.12 mole) by the method of Alder and Stein;[95] yield (12.0 g, 0.09 mole, 67.5%), as a colourless liquid b.p. 132-134° at 18 mm Hg. (Lit.[95] b.p. 129-130° at 13 mm Hg).

4.2.2.2. Norborn-5-en-2-endo,3-endo-yldicarboxylic acid anhydride (92).—



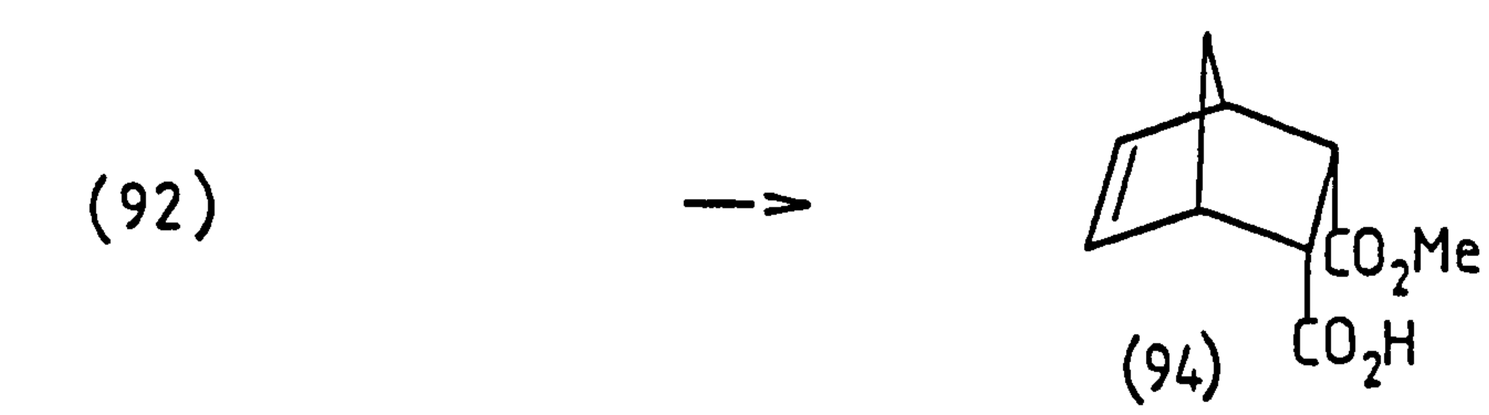
The anhydride (92) was prepared from reaction between cyclopentadiene (12 ml) and maleic anhydride (12.0 g, 0.12 mol) in ethyl acetate, using the method of Fieser;[96] yield (11.18g, 0.07 mole, 55.7%) as a white crystalline solid m.p. 164-166° (Lit.[96] m.p. 164°).

4.2.2.3. Norborn-5-en-2-endo,3-endo-yldicarboxylic acid (93).-



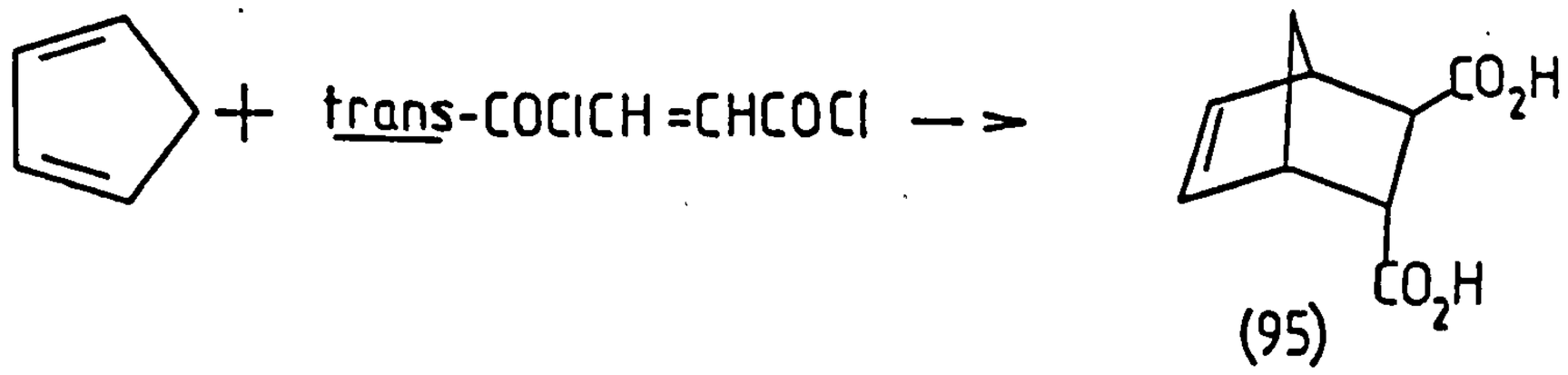
The endo, cis-acid (93) was prepared from the anhydride (92), (8.0 g, 0.08 mole) and water (100 ml), as reported by Fieser;[96] yield (7.80 g, 0.04 mole, 87.9%), as a white crystalline solid, m.p. 192-194° (Lit.[96] m.p. 177-179°), (Lit.[112] m.p. 193-194°).

4.2.2.4. Norborn-5-en-3-endo-carbomethoxy-2-endo-ylcarboxylic acid (94).-



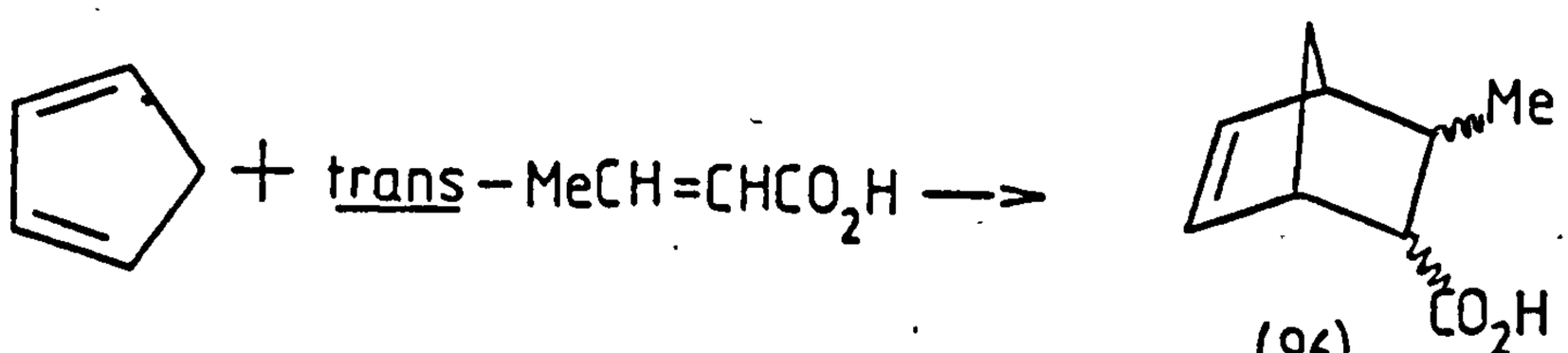
The half-ester (94), was prepared from the anhydride (92). (50.0g, 0.31 mole), and methanol (12.95 g, 0.41 mole) by the method of Walton;[98] yield (54.14 g, 0.28 mole, 90.59%) as a white crystalline solid, m.p. 103-105°. (Lit.[98] m.p. 103.5 - 105°, 87.30%), (Lit.[113] m.p. 102-103°).

4.2.2.5. Norborn-5-en-2-endo,3-exo-yldicarboxylic acid (95).—



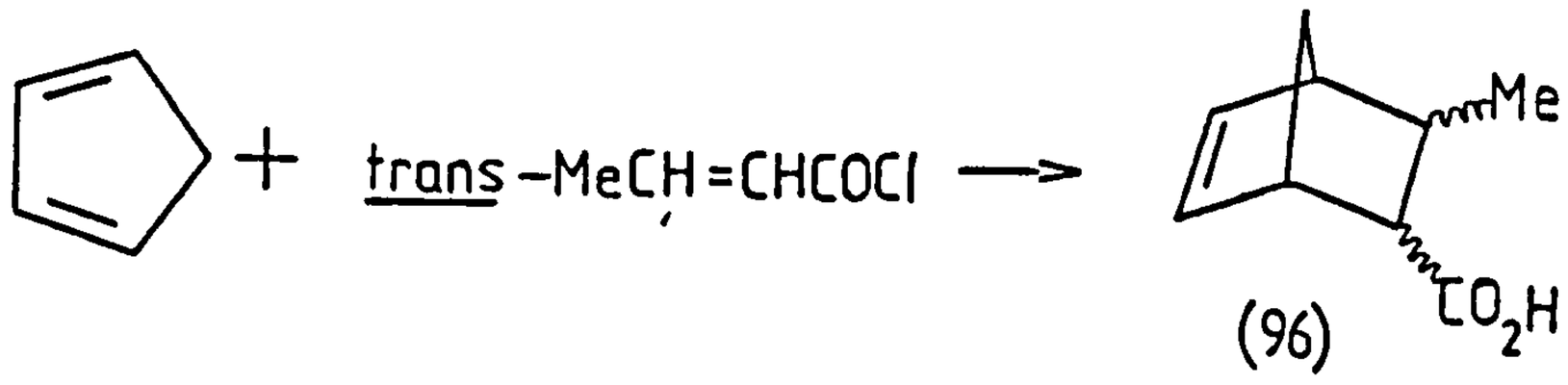
The trans-diacid (95) was prepared from cyclopentadiene (9.0 g, 0.14 mole) and fumaryl chloride (9.0 g, 0.06 mole) by the method of Alder and Stein;[95] yield (8.0 g, 0.04 mole, 73.4%), as a white crystalline solid, m.p. 188-190° (Lit.[95] m.p. 190°).

4.2.2.6. 3-Methylnorborn-5-en-2-ylcarboxylic acid (96).—



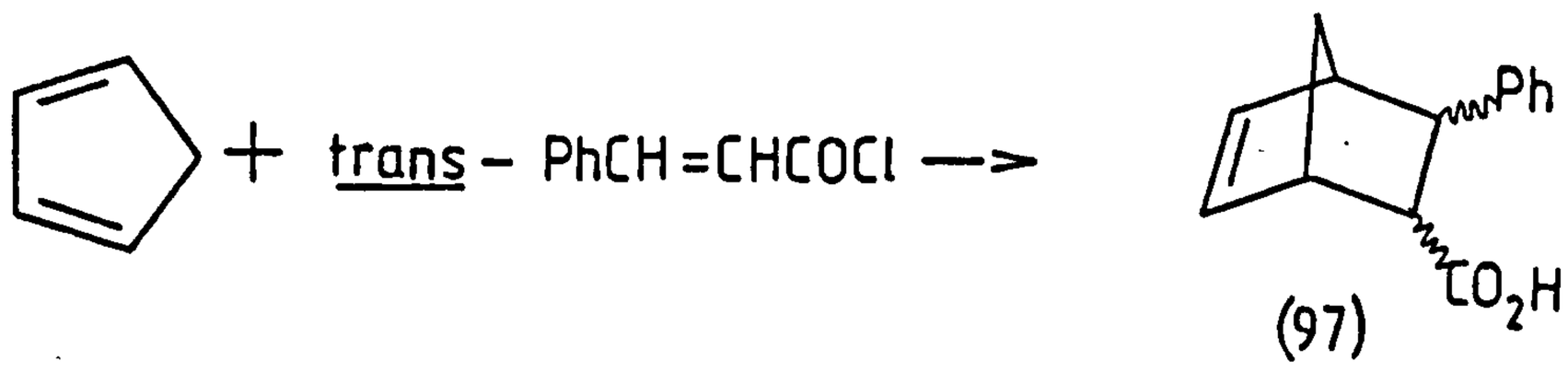
(i) The acid (96) (a mixture of endo and exo isomers) was prepared from cyclopentadiene (20.0 g, 0.31 mole) and trans-crotonic acid (22.2g ,0.26mole) by the method Komppa and Beckmann;[100] yield (8.0 g, 52.6 mole, 20.5%), b.p. 135-137° at 15 mm Hg, m.p. 93-95° (Lit.[100] b.p. 137-139°, m.p. 95°).

(ii)



The acid (96) also prepared from cyclopentadiene (20.0 g, 0.30 mole) and trans-crotonyl chloride (15.6 g, 0.15 mole), b.p. 120-124°, (Lit.[114] b.p. 120-123°) by the method of Alder and Stein;[95] yield (12.3 g, 81 mmole, 54.2%), m.p. 93-95° (Lit.[95] m.p. 95°).

4.2.2.7. 3-Phenylnorborn-5-en-2-ylcarboxylic acid (97).-



(97)

The acid (97) (a mixture of endo and exo isomers) was prepared from cyclopentadiene (16.0 g, 0.24 mole) and trans-cinnamoylchloride (12.50 g, 0.08 mole) by the method of Alder and Gunzl;[102] yield (8.70 g, 0.04 mole, 51%), as a white crystalline solid, m.p. 89-90° (Lit.[102] m.p. 90°).

4.2.2.8. Pent-3-enoic acid (98).-

$$MeCH_2CHO + HO_2CCH_2CO_2H \longrightarrow MeCH=CHCH_2CO_2H$$

(98)

The acid (98) was prepared from propionaldehyde (87.0 g, 1.50 mole) malonic acid (156.0 g, 1.5 mole) and dimethyl-aniline (181.5 g, 1.5 mole) by the method of Linstead;[103] yield (30.2 g, 0.3 mole) 20.13%), as a colourless oil, b.p. 120° at 30 mm Hg. (Lit.[103] b.p. 90° at 20 mm Hg).

4.2.2.9. Methyl Pent-3-enoate (99).-

$$MeCH{=}CHCH_2CO_2H \longrightarrow {}^{5}Me{}^{4}CH{=}{}^{3}CH{}^{2}CH_2{}^{1}CO_2Me$$

(98) (99)

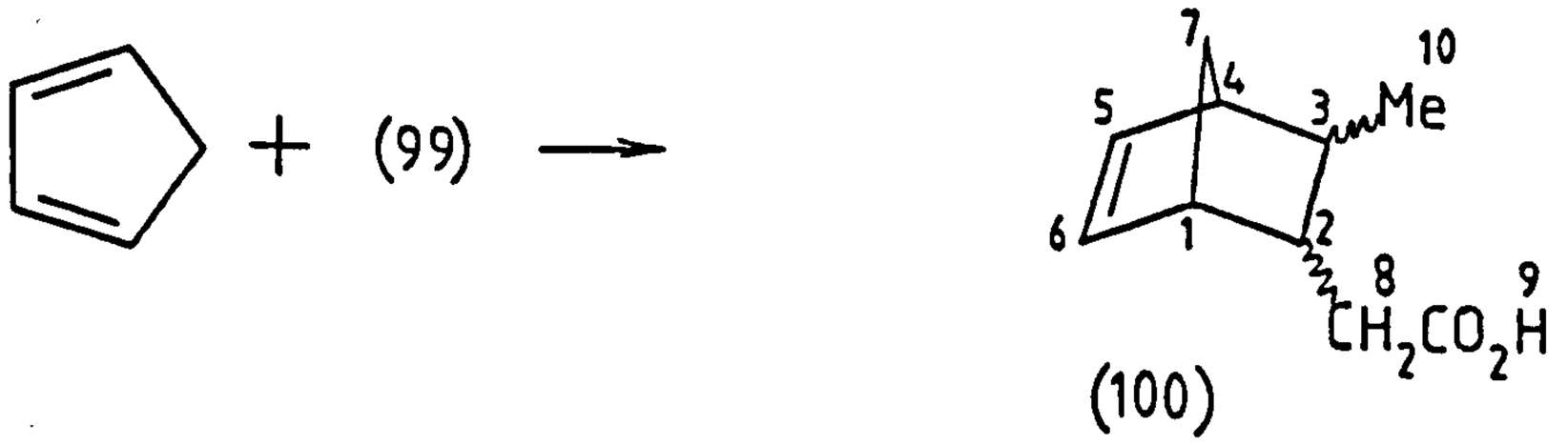
Pent-3-enoic acid (98) (25.0 g, 0.25 mole) and a 5% (v/v) solution (100 ml) of sulphuric acid in methanol was heated at reflux for 16 h. The solution was cooled to room temperature, diluted with water (100 ml) and extracted with ether (3 x 75 ml). The combined ether extracts were washed with sodium hydrogen carbornate solution (0.1 N) (2 x 50 ml), water (50 ml), dried ($MgSO_4$), filtered and evaporated in vacuo to afford a yellow oil. The oil was distilled under reduced pressure to give the ester (99) (27.80 g, 0.24 mole, 97.54%), b.p. 30° at 18 mm Hg. (Lit.[115] b.p. 128.1-128.3 at 635 mm Hg).

νmax cm^{-1} ($CHCl_3$), 1730 (S, C = O);

δ(60 MHz, $CDCl_3$) 5.50 (m, H-3, H-4), 3.62 (S, H-1), 3.0 (m, H-2), 1.68 (q, H-5);

J(Hz) (5,4)3, (5,3)1.

4.2.2.10. 3-Methylnorborn-5-en-2-ylacetic acid (100).-



(100)

A mixture of cyclopentadiene (1.80 g, 27.3 mmol) and the ester (99) (2.65 g, 23.3 mmol) were heated in a sealed tube at 180° for 72 h. The tube was cooled and opened, ether (50 ml) was added, the insoluble polymeric material

removed by filtration, and the ether solution filtrate evaporated to give a viscous yellow oil. The oil was mixed with 5% (w/w) solution of sodium hydroxide (60 ml), and the mixture heated at reflux for 4 h. The resulting solution was cooled and extracted with ether (2 x 20 ml), acidified to pH = 3 and extracted again with ether (5 x 20 ml). The combined ether extracts were washed with water (2 x 20 ml), dried ($MgSO_4$), filtered, and evaporated in vacuo to afford a brown oil. The oil was distilled under reduced pressure to give pent-3-enoic acid (98), (0.60 g, 5.9 mmol) b.p. 35° at 0.3 mm Hg and 3-methyl-norborn-5-end-2-ylacetic acid (100) (0.20 g, 1.2 mmol, 5.6%), as a colourless oil, b.p. 150-152° at 0.3 mm Hg.

νmax cm^{-1} ($CHCl_3$) 3200 (br, COOH), 1710 (S, C = O);
δ(60 MHz, $CDCl_3$) 9.63 (s, H-9), 6.10 (m, H-5, H-6), 2.80 (brs, H-1), 2.40 (brs, H-4), 2.20 (m, H-8), 2.0 (m, H-2), 1.80 (m, H-7anti, H-7syn, H-3), 1.08 (brs, H-10),
$M^{+\cdot}$ 168, ($M^{+\cdot}$ - CH_3) 153, ($M^{+\cdot}$ - CH_3COOH) 108.

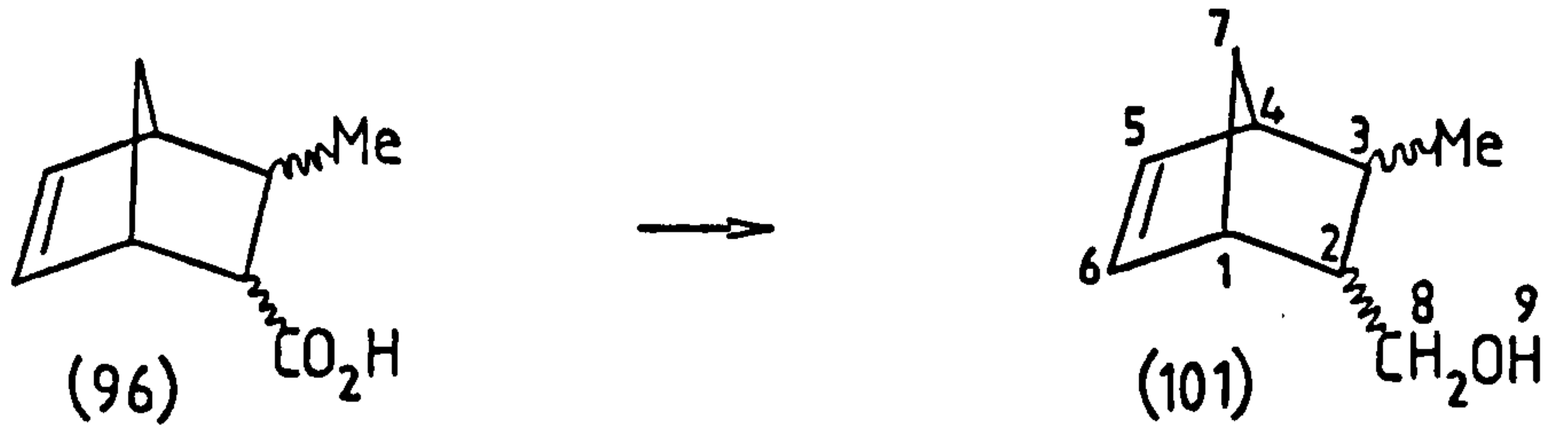
Method (ii)

A mixture of cyclopentadiene (5.03 g, 0.08 mole) and methyl pent-3-enoate (99) (8.70 g, 0.08 mole) were heated in a sealed tube at 180° for 200 h. The product was worked up as in Method (i) to afford 3-methylnorborn-5-en-2-ylacetic acid (100) (1.30 g, 8.4 mmol, 10.6%) b.p. 150-152° at 0.3 mm Hg. The ir and nmr data were identical to that reported in method (i).

Method (iii)

A 4-step reaction was followed, using 3-methylnorborn-5-en-2-ylcarboxylic acid (96) as a starting material;

Step 1: 3-Methylnorborn-5-en-2-ylmethanol (101).—



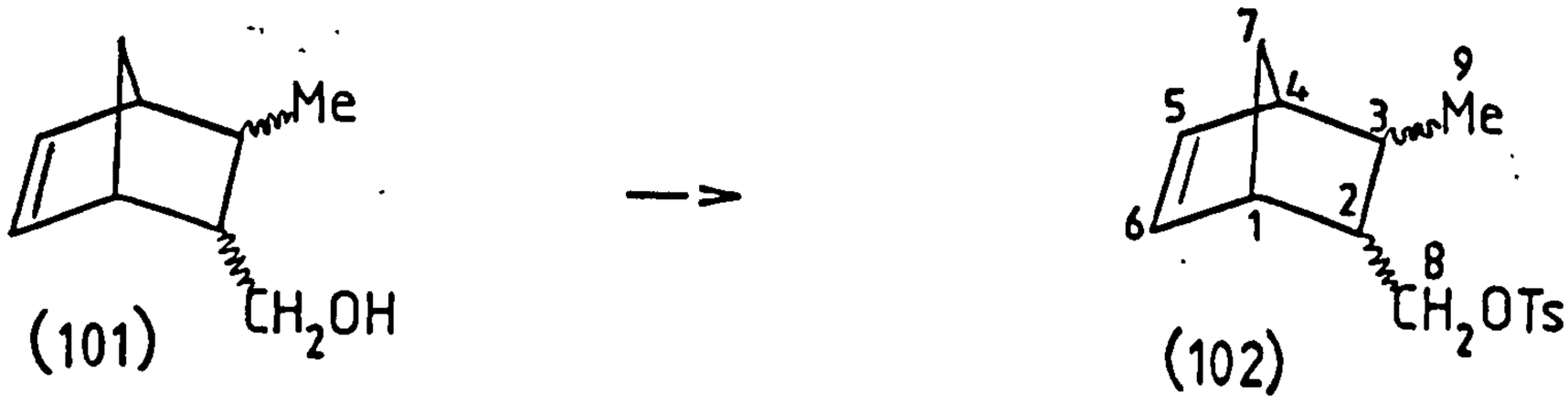
To a stirred suspension of lithium aluminum hydride (0.2 g, 5.4 mmol) in ether (50 ml) was slowly added a solution of the acid (96) (a mixture of endo and exo isomers) (0.6 g, 3.9 mmol) in ether (5 ml). The mixture was further stirred at room temperature for 1 h and then a saturated solution of ammonium chloride was slowly added until a granular precipitate was formed. The precipitate was filtered, washed with ether (20 ml), the combined filtrate and ether washing were dried ($MgSO_4$), filtered and the solvent evaporated to afford 3-methylnorborn-5-en-2-ylmethanol (101), (0.30 g, 2.2 mmol, 70.4%) as a colourless oil;

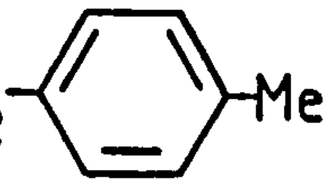
νmax cm^{-1} ($CHCl_3$) 3600 (m, OH), 1600 (w, C = C);

δ(60 MHz, $CDCl_3$) 6.1 (m, H-5, H-6), 3.30 (m, H-8), 3.0 (brs, H-9), 2.80 (m, H-1), 2.40 (m, H-4), 1.70 (m, H-7anti, H-7syn), 1.42 (brs, H-3), 1.10 (brs, H-2);

$M^{+\cdot}$ 138, ($M^{+\cdot}$ - CH_3) 123, ($M^{+\cdot}$ - H_2O) 120,

Step 2: <u>3-Methylnorborn-5-en-2-ylmethyl tosylate (102)</u>.—



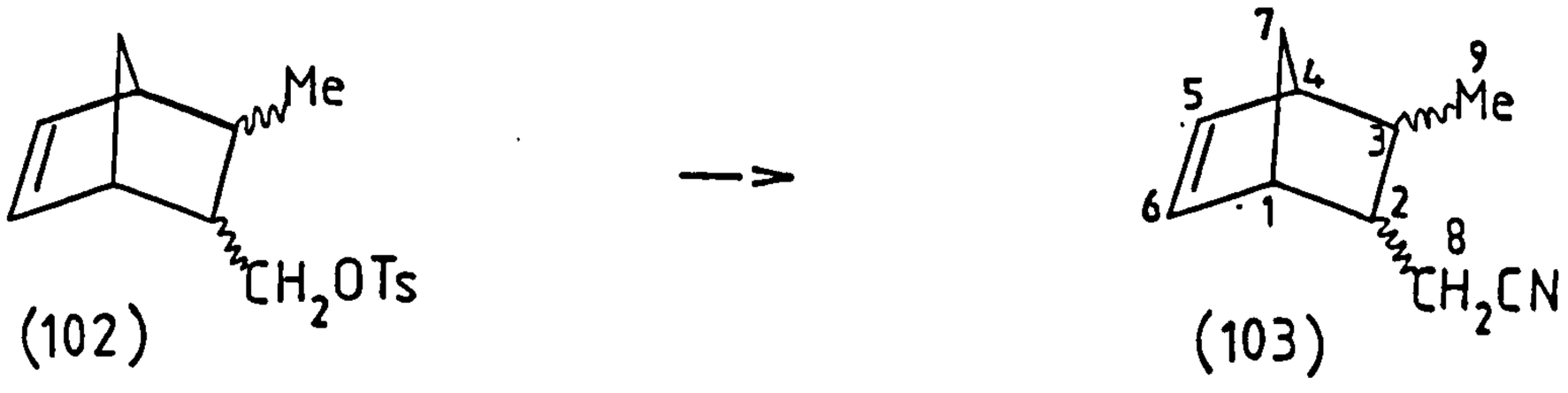
Ts = 

To a stirred solution of the alcohol (101) (a mixture of <u>endo</u> and <u>exo</u> isomers), (0.38 g, 2.75 mmol) in pyridine (8 ml) in an ice-salt bath was slowly added tosyl chloride (1.38 g, 7.25 mmol). The homogenous yellow solution was kept stirred for 0.5 h after the addition was completed and then left in the refrigerator for 60 h during which time white crystals of pyridinium hydrochloride gradually formed. The mixture was poured into ice-water (30.0 g), and the aqueous suspension resulting extracted with ether (4 x 30 ml). The combined ether extracts were washed with 50% (v/v) solution of hydrochloric acid (2 x 20 ml), water (2 x 20 ml), dried ($MgSO_4$), filtered and the solvent evaporated to afford <u>3-methylnorborn-5-en-2-ylmethyl tosylate</u> (102), (0.73 g, 2.6 mmol, 95.3%) as a yellow oil.

νmax cm^{-1} ($CHCl_3$) 1600 (m, aromatic);

δ(60 MHz, $CDCl_3$) 7.75 (d, aromatic), 7.35 (d, aromatic), 5.90 (dxq, H-5, H-6), 3.70 (dxq, H-8), 2.80 (m, H-1), 2.40 (s, H-10), 2.32 (brs, H-4), 1.80 (m, H-7<u>anti</u>, H-7<u>syn</u>) 1.40 (brs, H-3), 1.10 (brs, H-9); J(Hz) (<u>ortho</u>-Aromatic-H, <u>meta</u>-Aromatic-H) 8, (H-8a, H-8b) 15; M^+ 276, ($M^+ - CH_3$) 261, ($M^{+\cdot} - 2CH_3$) 246, ($M^{+\cdot} - C_7H_7SO_2OH$) 108.

Step 3: <u>3-Methylnorborn-5-en-2-ylmethyl cyanide (103)</u>.–



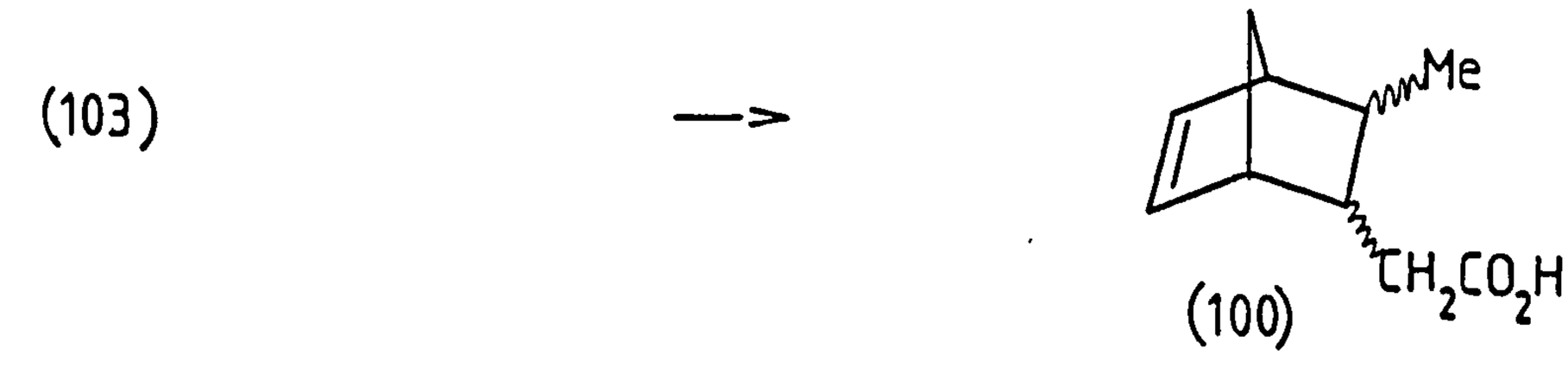
To a solution of the tosylate (102) (a mixture of <u>endo</u> and <u>exo</u> isomers), (0.72 g, 2.62 mmol) in anhydrous DMSO (5 ml) was added potassium cyanide (0.2g, 3.1mmol). The mixture was slowly stirred and heated at 80° for 15 h, cooled to room temperature and then poured into brine solution (30 ml). The mixture resulting was extracted with chloroform (4 x 30 ml), the combined extracts were washed with brine solution (2 x 20 ml) and water (20 ml), dried ($MgSO_4$), filtered and the solvent evaporated to give <u>3-methylnorborn-5-en-2-ylmethyl cyanide</u> (103), (0.30 g, 2.04 mmol, 78%) as a brown oil.

νmax cm^{-1} (CCl_4) 2250 (m, C ≡ N);

δ(60 MHz, $CDCl_3$) 6.15 (m, H-5, H-6), 2.80 (m, H-1), 2.30 (m, H-8, H-4), 1.80 (m, H-7<u>anti</u>, H-<u>syn</u>), 1.50 (brs, H-3), 1.10 (brs, H-9);

$M^{+\cdot}$ 147, ($M^{+\cdot}$ - CH_3) 132, ($M^{+\cdot}$ - HCN) 120.

Step 4: <u>3-Methylnorborn-5-en-2-ylacetic acid (100)</u>.–



The cyanide (103) (a mixture of endo and exo isomers) (0.30 g, 2.04 mmol) was added to a solution of potassium hydroxide (0.6 g, 9 mmol) in water (3 ml). The solution was heated at 100° for 72 h, cooled and diluted with water (5 ml), the resulting alkaline solution was extracted with ether (2 x 10 ml), acidified to pH = 3 and extracted again with chloroform (5 x 10 ml). The combined chloroform extracts were washed with water (2 x 10 ml), dried ($MgSO_4$), filtered and evaporated in vacuo to afford an oil. The oil was distilled using a Buchi GKR-50 to give 3-methylnorborn-5-en-2-ylacetic acid (100) (0.24 g, 1.6 mmol, 77%) as a colourless oil b.p. 150° at 0.3 mm Hg. The nmr, ir and mass spectra were identical as 4.2.2.10 (Method i). The overall yield from Step 1 to Step 4 was 40%.

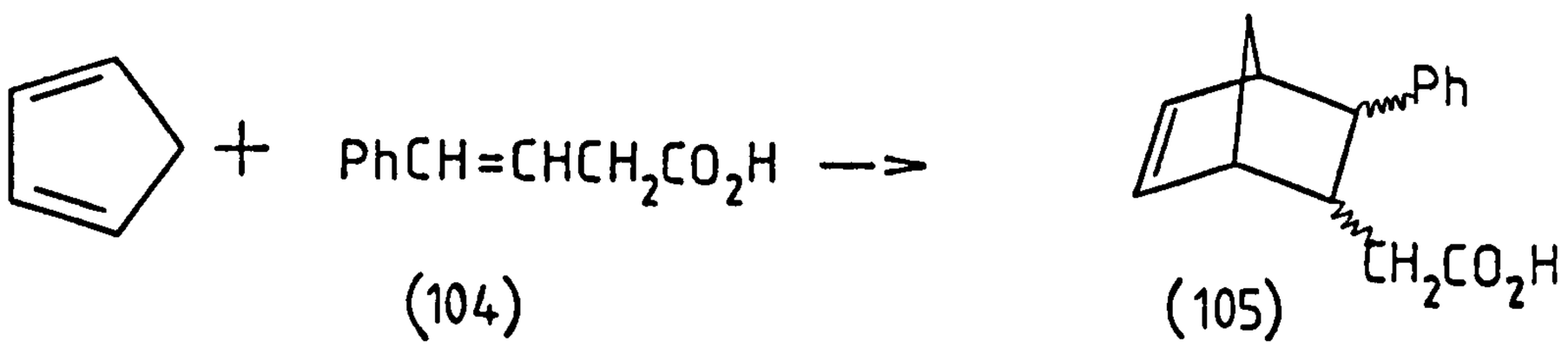
4.2.2.11. 4-Phenylbut-3-enoic acid (104).—

$$HO_2CCH_2CO_2H + PhCH_2CHO \longrightarrow PhCH{=}CHCH_2CO_2H$$
(104)

The acid (104) was prepared from malonic acid (30.0g, 0.26 mol), phenylacetaldehyde (36.0 g, 0.30 mole) and diethylamine (10 drops) by the method of Linstead;[105] yield (20.3g, 0.13 mole, 41.76%) as a white crystalline solid, m.p. 85-87°. (Lit.[105] m.p. 87°).

4.2.2.12. 3-Phenylnorborn-5-en-2-ylacetic acid (105).-

Method (i)

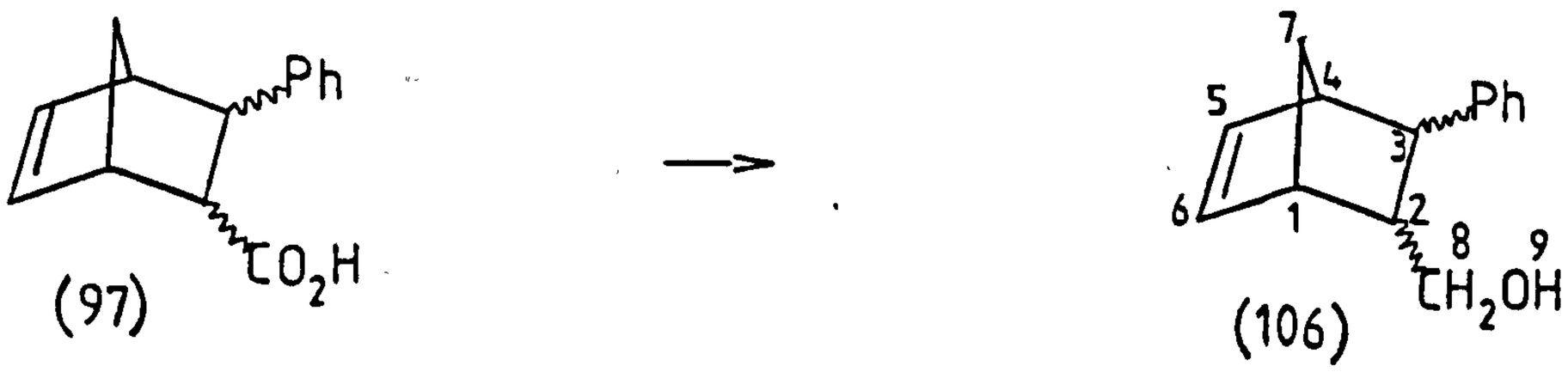


A mixture of cyclopentadiene (3.30 g, 0.05 mole) and the acid (104) (4.0 g, 0.03 mole) was heated in a sealed tube at 180° for 30 h. The tube was cooled and opened, the contents diluted with ether (50 ml) and extracted with sodium hydrogen carbornate (0.5 N) (4 x 30 ml). The combined bicarbornate extracts were washed with ether (2 x 30 ml), and acidified to pH = 3, the acidified solution was then extracted with ether (4 x 30 ml) and these ether extracts combined and washed with water (30 ml), dried ($MgSO_4$), filtered, and the solvent evaporated to give unchanged acid (104) (3.10 g, 0.02 mole), as a white solid m.p. 85-87°.

Method (ii)

A 4-step reaction was carried out using 3-phenylnorborn-5-en-2-ylcarboxylic acid (97) as a starting material.

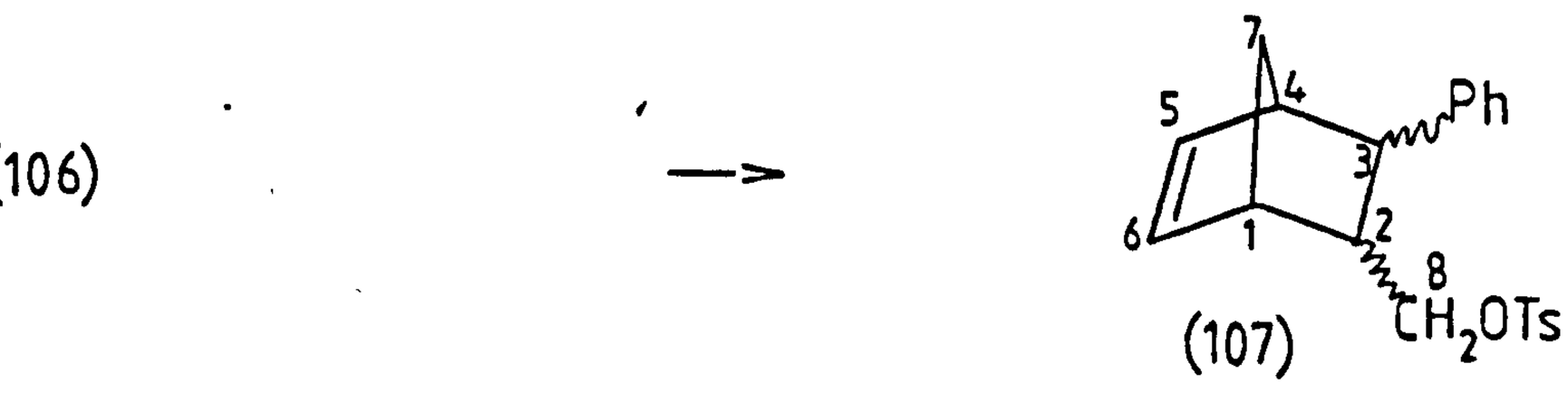
Step 1: <u>3-Phenylnorborn-5-en-2-ylmethanol (106)</u>.-



The solution of acid (97) (a mixture of <u>trans</u>-<u>endo</u> and <u>trans</u>-<u>exo</u> isomers) (7.0 g, 0.03 mole) in anhydrous ether (22 ml) was added slowly over 1 h to a stirred suspension of lithium aluminum hydride (2.0 g, 0.05 mole) in ether (400 ml). The reaction was stirred for a further 1 h after the addition was completed and a saturated solution of ammonium chloride added until a granular precipitate formed. The precipitate was removed by filtration, the filtrate dried ($MgSO_4$), filtered and solvent evaporated to give <u>3-phenylnorborn-5-en-2-ylmethanol</u> (106), (5.3 g, 0.03 mole, 81.04%), as a yellow oil;

νmax cm^{-1} ($CHCl_3$) 3400 (m, OH), 1600 (m, aromatic); δ(60 MHz, $CDCl_3$) 7.15 (m, C_6H_5), 6.15 (m, H-5, H-6), 3.50 (dxq, H-8), 2.90 (m, H-4, H-1, H-9), 2.10 (m, H-2, H-3), 1.60 (m, H-7<u>anti</u>, H-7<u>syn</u>); J(Hz) (8a, 8b) 10; M^+ 200, ($M^{+\cdot} - H_2O$) 182, ($M^{+\cdot} - CH_3OH$) 168, ($M^{+\cdot} - C_6H_5$) 123.

Step 2: <u>3-Phenylnorborn-5-en-2-ylmethyl tosylate (107)</u>.-



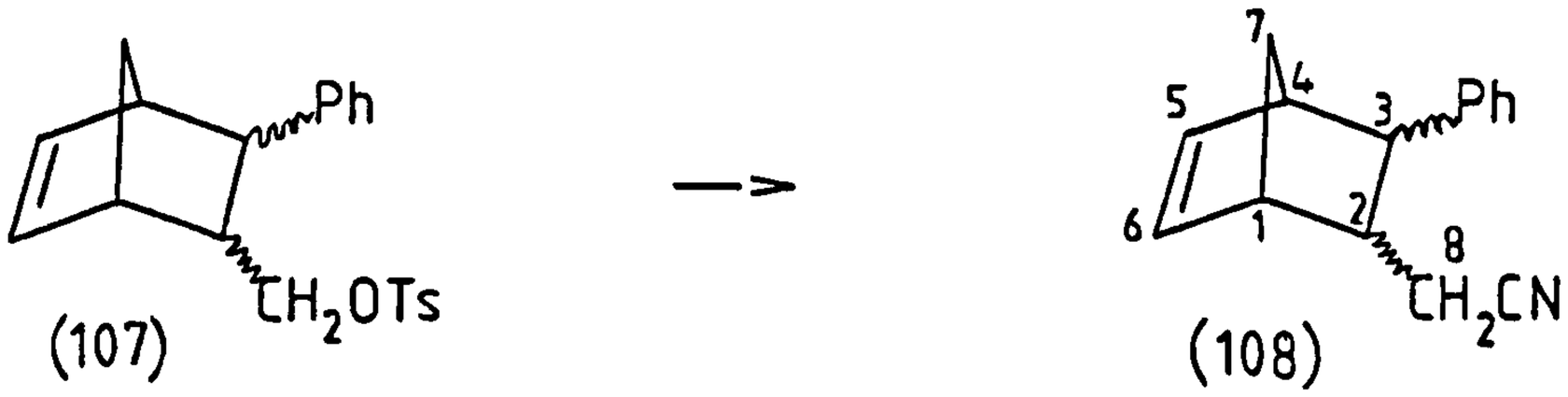
The solution of alcohol (106) (a mixture of trans-endo and trans-exo isomers) in pyridine (60 ml) was cooled and stirred in ice-salt bath. Tosyl chloride (7.6 g, 0.04 mole) was added slowly and the resultant yellow solution kept in a refrigerator for 40 h. The product was worked up as 4.2.2.10 Method (iii), Step 2, to give 3-phenylnorborn-5-en-2-ylmethyl tosylate (107), (6.9 g, 0.02 mole, 78%) as an oil.

νmax cm^{-1} ($CHCl_3$) 1600 (m, aromatic);

δ(60 MHz, $CDCl_3$) 7.75 (d, aromatic), 7.25 (d, aromatic), 7.18 (brs, C_6H_5), 6.10 (m, H-5, H-6), 4.0 (dxq, H-8), 2.90 (brd, H-4, H-1), 2.35 (s, CH_3), 2.40 (brs, H-3), 2.0 (m, H-2), 1.52 (m, H-7anti, H-7syn);

J(Hz) (ortho-Aromatic-H, meta-Aromatic-H) 8, (8a, 8b) 12; $M^{+\cdot}$ 354, ($M^{+\cdot}$ $-CH_3$) 339, ($M^{+\cdot}$ - C_6H_5) 277.

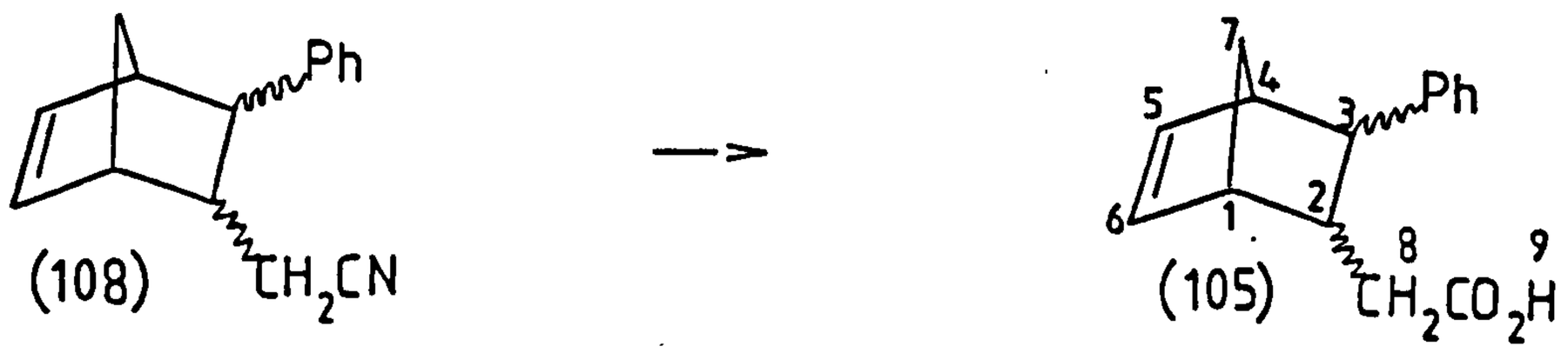
Step 3: 3-Phenylnorborn-5-en-2-ylmethyl cyanide(108) .-



Potassium cyanide (2.0 g, 0.03 mole) was added to a solution of the tosylate (107) (a mixture of trans-endo and trans-exo isomers) (6.7 g, 0.019 mole) in DMSO (40 ml). The mixture was stirred and heated at 100° for 16 h and worked up as in 4.2.2.10. Method (iii), Step 3, to give 3-phenylnorborn-5-en-2-ylmethyl cyanide (108) (3.33 g, 0.02 mole, 81.8%) as a yellow oil.

νmax cm^{-1} ($CHCl_3$) 2250 (m, C ≡ N), 1600 (m, aromatic);
δ(60 MHz, $CDCl_3$) 7.20 (m, C_6H_5), 6.25 (m, H-5, H-6),
3.0 (brs, H-4), 2.75 (brs, H-1), 2.25 (m, H-8, H-2),
1.70 (m, H-7anti, H-7syn);
$M^{+\cdot}$ 209, ($M^{+\cdot}$ - HCN) 182, ($M^{+\cdot}$ - CH_3CN) 168, ($M^{+\cdot}$ - C_6H_5) 132.

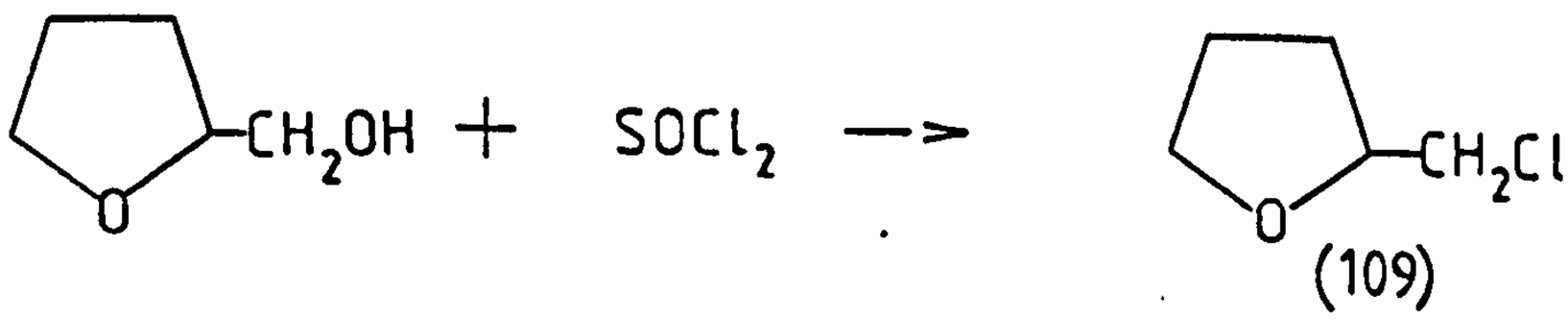
Step 4:



A solution of the cyanide (108) (a mixture of trans-endo and trans-exo isomers) (3.20 g, 0.015 mole) in aqueous potassium hydroxide [10.0 g KOH in water (100 ml)] was stirred and heated at 100° for 60 h. It was worked up as in 4.2.2.10. Method (iii), Step 4 to give a yellow oil; the oil was distilled under reduced pressure to afford 3-phenylnorborn-5-en-2-ylacetic acid (105) (2.80 g, 0.012 mole, 77.1%) as a colourless oil, b.p. 140° at 0.2 mm Hg. Found: C, 78.90; H, 6.98. $C_{15}H_{16}O_2$ requires C, 78.95; H, 7.02%;

νmax cm^{-1} ($CHCl_3$) 3500-2400 (m, COOH),
1710 (s, C = O), 1600 (m, aromatic);
δ(60 MHz, $CDCl_3$) 11.50 (s, H-9), 7.20 (m, C_6H_5),
6.20 (m, H-5, H-6), 2.98 (brs, H-4), 2.80 (m, H-3),
2.60 (m, H-1), 2.35 (dxq, H-8), 2.10 (m, H-2),
1.65 (m, H-7anti, H-7syn);
J(Hz) (8a, 8b) 12;
$M^{+\cdot}$ 228, ($M^{+\cdot}$ - C_6H_5) 151, ($M^{+\cdot}$ - CH_3COOH) 160.

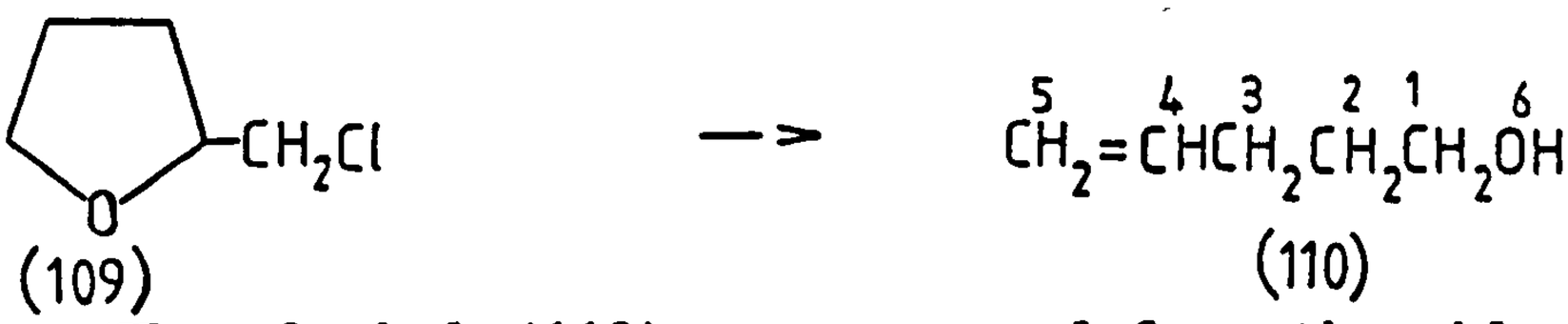
4.2.2.13. Tetrahydrofurfuryl chloride (109).-



(109)

The chloride (109) was prepared from tetrahydrofurfuryl alcohol (100 g, 0.98 mole) and thionyl chloride (122.5 g, 1.03 mole) in pyridine (85.3 g, 1.1 mole) by the method of Brooks and Snyder;[106] yield (42.3 g, 0.35 mole, 36%) as a colourless liquid, b.p. 47-48° at 15 mm Hg. (Lit.[106] b.p. 41-42 at 11 mm Hg).

4.2.2.14. Pent-4-en-1-ol (110).-



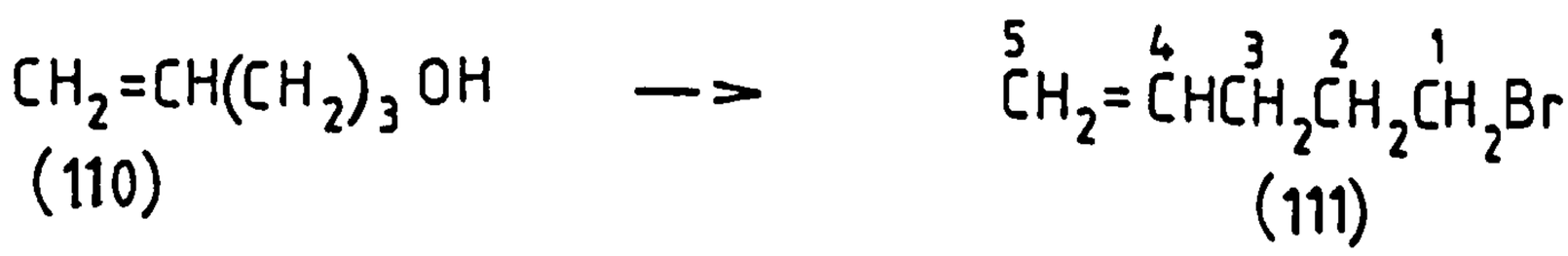
(110)

The alcohol (110) was prepared from the chloride (109) (25.0 g, 0.21 mole) and powdered sodium (12.0 g, 0.52 mole) by the method of Brooks and Snyder;[106] yield (11.0 g, 0.13 mole, 63%), as a colourless liquid, b.p. 42-43° at 10 mm Hg. (Lit.[106] b.p. 134-137° at N. atm.)

νmax cm^{-1} ($CHCl_3$) 3500 (m, OH);

δ(60 MHz, $CDCl_3$) 5.80 (dx sextet, H-4), 5.0 (m, H-5), 3.65 (t, H-1), 2.15 (m, H-3), 2.0 (brs, H-6), 1.75 (m, H-2).

4.2.2.15. 1-Bromopent-4-ene (111).-



(110) (111)

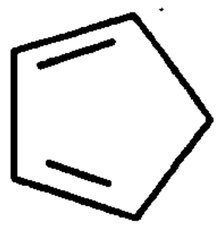
The bromide (111) was prepared from pent-4-en-1-ol (110) (2.0 g, 23 mmole) in pyridine (0.6 g, 7.5 mmole) and phosphorus tribromide (2.6 g, 9.6 mmole) by the method of Laforge;[107] yield (2.50 g, 16.8 mmole, 72.3%), as a colourless liquid, b.p. 130° at 760 mm Hg. (Lit.[107] b.p. 130° at 760 mm Hg; 81.5%).

4.2.2.16. Hex-5-enoic acid (112). –

$$\underset{(111)}{CH_2=CH(CH_2)_3Br} \longrightarrow \underset{(112)}{CH_2=CH(CH_2)_3CO_2H}$$

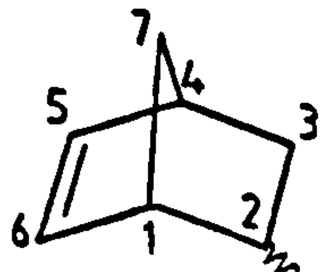
Magnesium turnings (1.31 g, 53.6 mmole) were covered with anhydrous ether (50 ml) and cooled to 0° in ice-bath. A solution of 1-bromopent-4-ene (117) (8 g, 53.6 mmole) in ether (20 ml) was added dropwise over 1 h with continuous stirring to give a clear solution of pent-4-enylmagnesium bromide. The ice bath was removed and small pieces of dry ice (28 g) were added, the mixture was stirred for 0.5 h and water (60 ml) then added. The solution was acidified, the ether layer was separated and the aqueous layer was extracted with ether (3 x 30 ml). The combined ether layer and extracts were dried ($MgSO_4$) and evaporated and the product was distilled to give hex-5-enoic acid (112), (3.6 g, 31.6 mmole, 58.8%), as a colourless liquid, b.p. 103-105° at 13 mm Hg. (Lit.[108] b.p. 101-102° at 8 mm Hg).

4.2.2.17. Norborn-5-en-2-ylpropanol (113).—



+ $CH_2=CH(CH_2)_3OH$ —>

(110)



(113) $CH_2CH_2CH_2OH$

A mixture of cyclopentadiene (15.4 g, 0.2 mole) and pent-4-en-1-ol (110) (10 g, 0.12 mole) was heated in a sealed tube at 180° for 60 h. The tube was cooled and opened, the product was distilled to give Norborn-5-en-2-ylpropanol (113) (6.2 g, 0.04 mole, 35.2%), as a colourless liquid, b.p. 79-80° at 0.08 mm Hg.

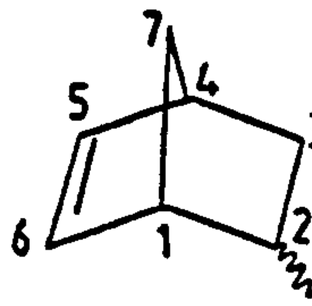
νmax cm^{-1} ($CHCl_3$) 3500 (m, OH);

δ(60 MHz, $CDCl_3$) 6.0 (m, H-5, H-6), 3.85 (s, H-11), 3.50 (t, H-10), 2.75 (m, H-1, H-4), 2.5-0.8 (m, H-2, H-7b, H-7a, H-8, H-9, H-3exo), 0.5 (m, H-3endo);

$M^{+\cdot}$ 152, ($M^{+\cdot}$ - H_2O) 134, ($M^{+\cdot}$ - C_3H_7OH) 102.

4.2.2.18. Norborn-5-en-2-ylpropyl tosylate (114).—

(113) —>



(114) $CH_2CH_2CH_2OTs$

The solution of alcohol (113) (a mixture of endo and exo isomers) (6.0 g, 0.04 mole) in pyridine (90 ml) was cooled in an ice-bath and tosylchloride (15.0 g, 0.07 mole) added. The mixture was stirred and after 0.5 h a clear yellow solution obtained. The solution was kept in the

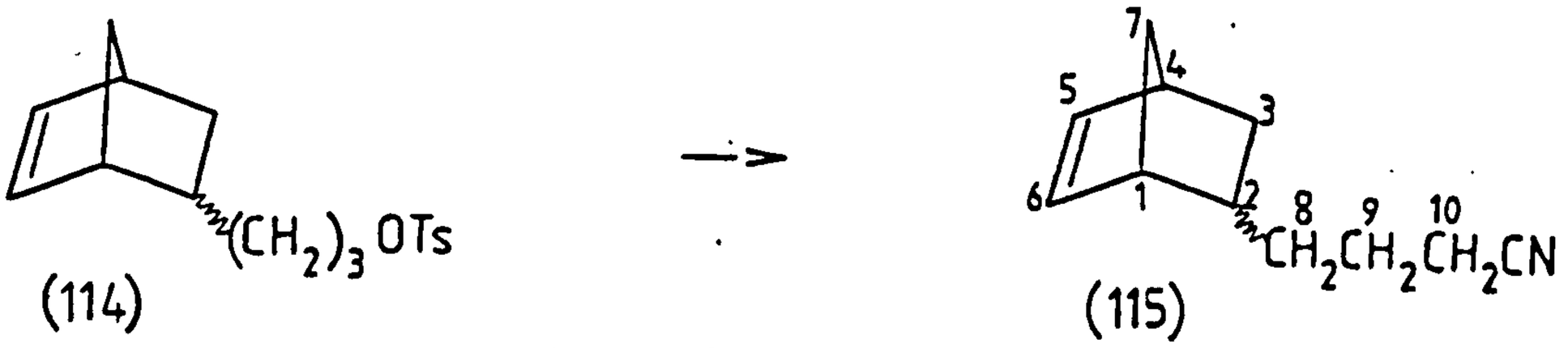
refrigerator for 16 h and worked up as in 4.2.2.10 Method (iii) Step 2 to give Norborn-5-en-2-ylpropyltosylate (114) (8.2 g, 0.03 mole, 67%), as a colourless liquid, b.p. 102-103° at 0.3 mm Hg.

νmax cm^{-1} ($CHCl_3$) 1600 (m, aromatic);

δ(60 MHz, $CDCl_3$) 7.80 (d, aromatic), 7.30 (d, aromatic), 6.0 (m, H-5, H-6, 4.0 (t, H-10), 2.75 (m, H-1, H-4), 2.45 (s, CH_3), 2.2-0.9 (m, H-7a, H-7b, H-8, H-9, H-2, H-3exo), 0.5 (m, H-3endo); J(Hz) (ortho-Aromatic-H, meta-Aromatic-H) 8;

$M^{+\cdot}$ 306, ($M^{+\cdot}$ - CH_3) 295, ($M^{+\cdot}$ - $C_7H_7SO_2OH$) 134.

4.2.2.19. Norborn-5-en-2-ylpropyl cyanide (115).



Potassium cyanide (2.3 g, 0.04 mole) was added to a solution of the tosylate (114) (a mixture of endo and exo isomers) (8.0 g, 0.03 mole) in DMSO (40 ml). The mixture was stirred and heated at 100° for 16 h and worked up as in 4.2.2.10 Method (iii) Step 3, to afford Norborn-5-en-2-ylpropyl cyanide (115) (3.15 g, 0.02 mole, 75.4%) as a yellow oil.

νmax cm^{-1}($CHCl_3$) 2250 (m, C ≡ N);

δ(60 MHz, $CDCl_3$) 6.1 (m, H-5,H-6), 2.72 (m, H-1, H-4), 2.25 (t, H-10), 2.0-0.8 (m, H-7a, H-7b, H-8, H-9, H-3exo, H-2), 0.5 (m, H-3endo);

$M^{+\cdot}$ 161, ($M^{+\cdot}$ - HCN) 134, ($M^{+\cdot}$ - HCN - C_3H_7) 91.

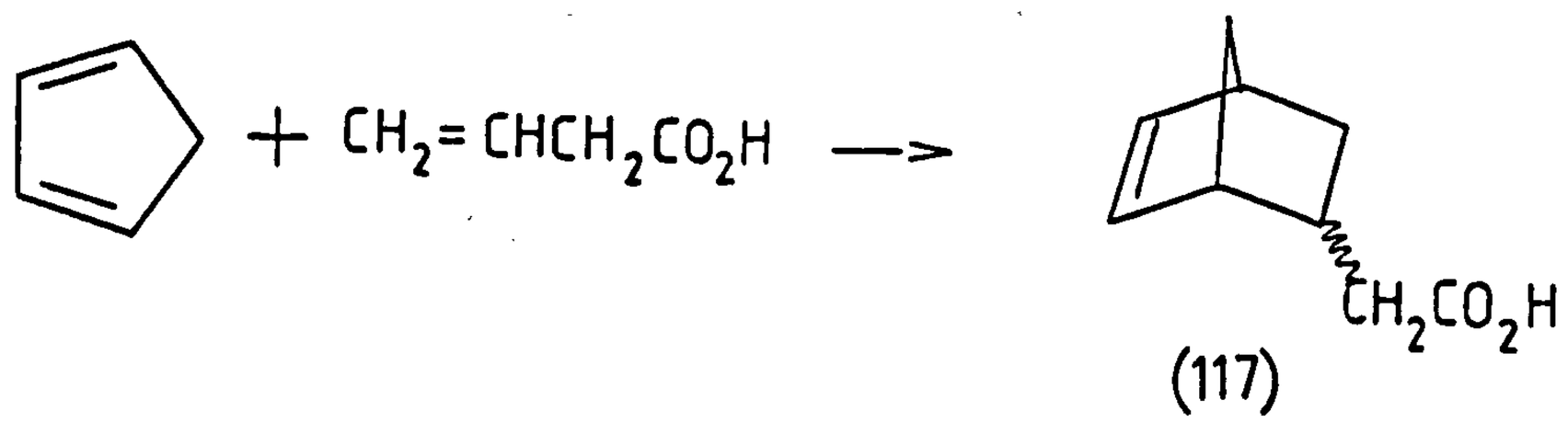
4.2.2.20. Norborn-5-en-2-ylbutanoic acid (116).—

The cyanide (115) (a mixture of endo and exo isomers) (3.1 g, 0.02 mole) in aqueous potassium hydroxide [10.0 g KOH in water (100 ml)] was stirred and heated at 110° for 60 h. The product was worked up as the 4.2.2.10. Method (ii), Step 4, to give Norborn-5-en-2-ylbutanoic acid (116) (2.51 g, 0.02, 72.7%) as a colourless liquid, b.p. 122-123° at 0.3 mm Hg.

Found: C, 73.16, H, 8.88 $C_{11}H_{18}O_2$ requires C, 73.33, H, 8.89%.

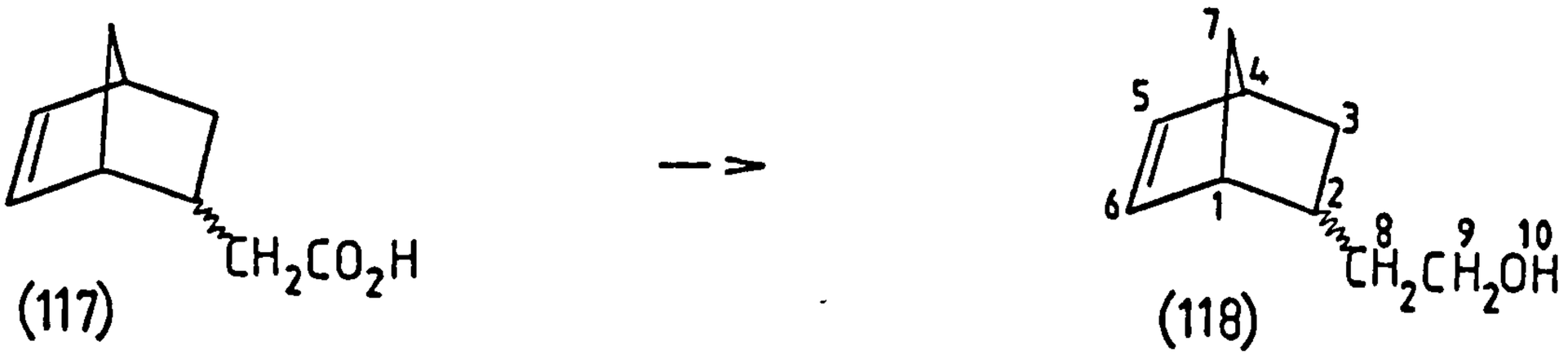
νmax cm^{-1} ($CHCl_3$) 3200 (m, COOH), 1710 (s, C = O), δ(60 MHz, $CDCl_3$) 11.55 (s, COOH), 6.0 (m, H-5, H-6), 2.75 (m, H-1, H-4), 2.30 (t, H-10), 2.10-1.0 (m, H-2, H-3exo, H-7, H-8, H-9), 0.5 (brd, H-3endo);
$M^{+\cdot}$ 180.

4.2.2.21. Norborn-5-en-2-ylacetic acid (117).—



The acid (117) (a mixture of <u>endo</u> and <u>exo</u> isomers) was prepared from cyclopentadiene (8.0 g, 0.12 mole) and vinylacetic acid (12.0 g, 0.14 mole) by the method of Alder and Windemuth;[109] yield (9.3 g, 0.06%, 62%) as a colourless liquid, b.p. 132-134° at 10 mm H. (Lit.[109] b.p. 137-139° at 12 mm Hg).

4.2.2.22. <u>Norborn-5-en-2-ylethanol (118)</u>.—



To a stirred suspension of lithium aluminum hydride (1.9 g, 0.05 mole) in ether (160 ml) was added dropwise a solution of acid (117) (3.0 g, 0.02 mole) in ether (30 ml). The mixture was stirred for 1 h after the addition was completed, and a saturated solution of ammonium chloride was then added until a granular precipitate formed. The precipitate was removed by filtration, the filtrate dried ($MgSO_4$) and the solvent evaporated to afford <u>Norborn-5-en-2-ylethanol</u> (118) (2.19 g, 0.02 mole) 83.7%) as a colourless liquid, b.p. 84-86° at 0.3 mm Hg.

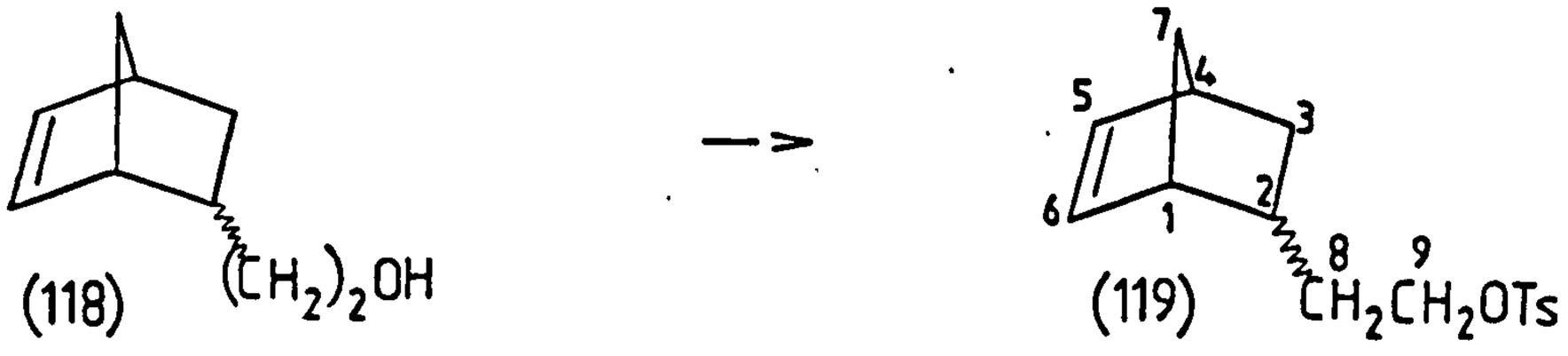
νmax cm^{-1} ($CHCl_3$) 3500 (m, OH);

δ(60 MHz, $CDCl_3$) 6.0 (m, H-5, H-6), 4.10 (brs, H-10), 3.50 (t, H-9), 2.72 (m, H-1, H-4), 2.0-0.8 (m, H-7a, H-7b, H-8, H-2, H-3<u>exo</u>), 0.5 (2 brd, H-3<u>endo</u>);

J(Hz) (3-<u>exo</u>, 3-<u>endo</u>) 12;

$M^{+\cdot}$ 138, ($M^{+\cdot} - H_2O$) 120, ($M^{+\cdot} - H_2O - C_2H_4$) 92.

4.2.2.23. Norborn-5-en-2-ylethyl tosylate (119).—



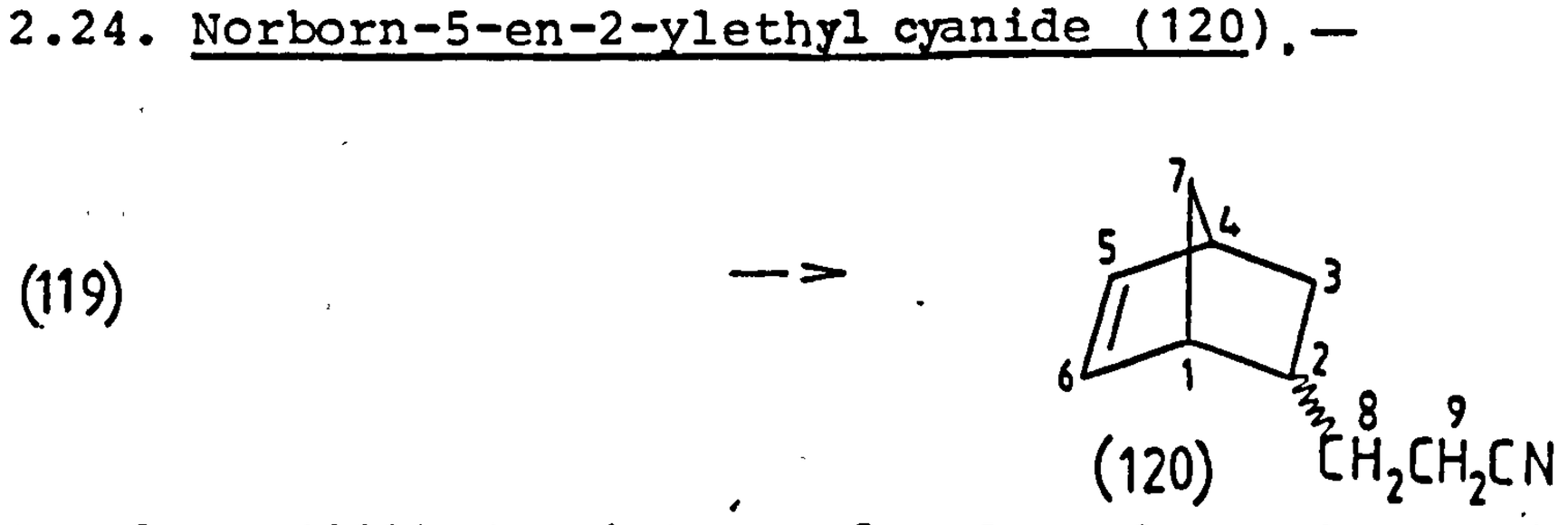
A solution of alcohol (118) (a mixture of exo and endo isomers) 2.0 g, 0.014 mole) in pyridine (46 ml) was cooled in an ice-bath and tosyl chloride (7.2 g, 0.03 mole) added. The mixture was stirred and after 0.5 h a clear yellow solution was obtained. The solution was kept in the refrigerator for 16 h and worked up as in 4.2.2.10 Method (iii), Step 2, to give Norborn-5-en-2-ylethyl tosylate (119) (3.8 g, 0.013 mole, 89.8%) as a yellow oil.

νmax cm^{-1} ($CHCl_3$) 1600 (m, aromatic);

δ(60 MHz, $CDCl_3$) 7.75 (d, aromatic), 7.30 (d, aromatic), 5.95 (m, H-5, H-6), 3.92 (t, H-9), 2.70 (brs, H-1, H-4), 2.43 (s, CH_3), 1.95-0.8 (m, H-7a, H-7b, H-2, H-3exo, H-8), 0.45 (2brd, H-3endo); J(Hz) (ortho-Aromatic-H, meta-Aromatic-H) 8, (3-exo, 3-endo) 12;

$M^{+\cdot}$ 292, ($M^{+\cdot}$ - CH_3) 277, ($M^{+\cdot}$ - $C_7H_7SO_2OH$) 120.

4.2.2.24. Norborn-5-en-2-ylethyl cyanide (120).—

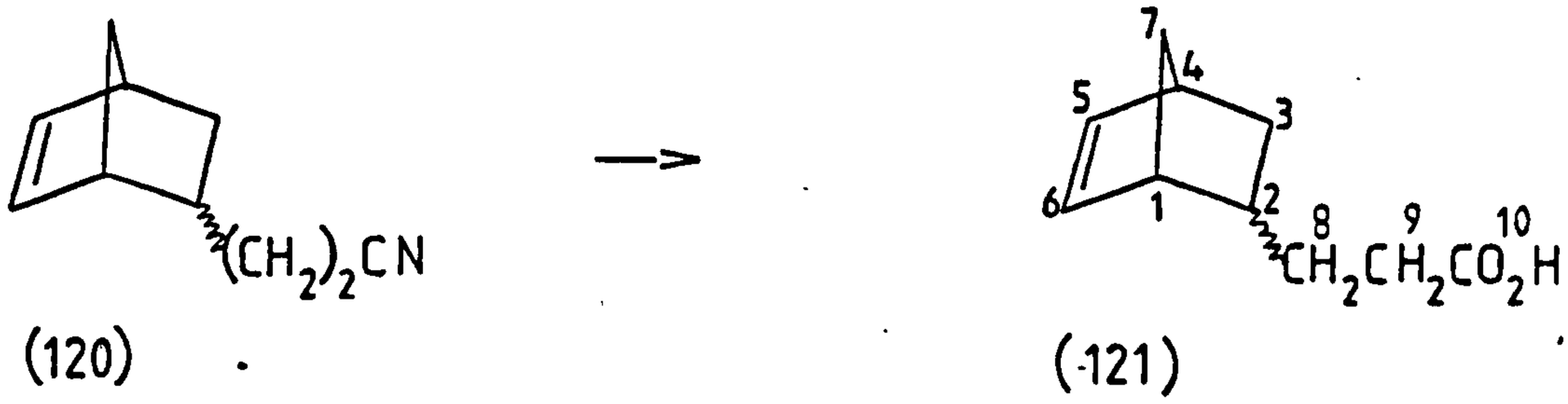


The tosylate (119) (a mixture of endo and exo isomers) (3.7 g, 12.7 mole) and powdered potassium cyanide (1.20 g,

1.80 mmole) in DMSO (35 ml) was stirred and heated at 100° for 16 h. The product was worked up as 4.2.2.10. Method (iii), Step 3 to give Norborn-5-en-2-ylethyl cyanide (120) (1.50 g, 10.2 mmol, 80.6%).

νmax cm^{-1} ($CHCl_3$) 2250 (m, C N);
δ(60 MHz, $CDCl_3$) 6.10 (m, H-5, H-6), 2.72 (m, H-1, H-4), 2.30 (t, H-9), 2.0-0.8 (m, H-7a, H-7b, H-2, H-3exo, H-8), 0.5 (2brd, H-3endo); J(Hz) (3-exo, 3-endo) 12; $M^{+\cdot}$ 147, ($M^{+\cdot}$ - HCN) 120.

4.2.2.25. Norborn-5-en-2-ylpropionic acid (121).—



(120) (121)

The cyanide (120) (a mixture of exo and endo isomers) (1.50 g, 10.2 mmole) in aqueous potassium hydroxide 5.0 g KOH in water (50 ml) was stirred and heated at 100° for 40 h. The product was worked up as in 4.2.2.10. Method (iii), Step 4, to give norborn-5-en-2-ylpropionic acid (121) (1.40 g, 8.43 mmole, 82.8%) as a colourless liquid, b.p. 115-117° at 0.3 mm Hg. (Lit.[93] b.p. 102-103° at 0.05 mm Hg).

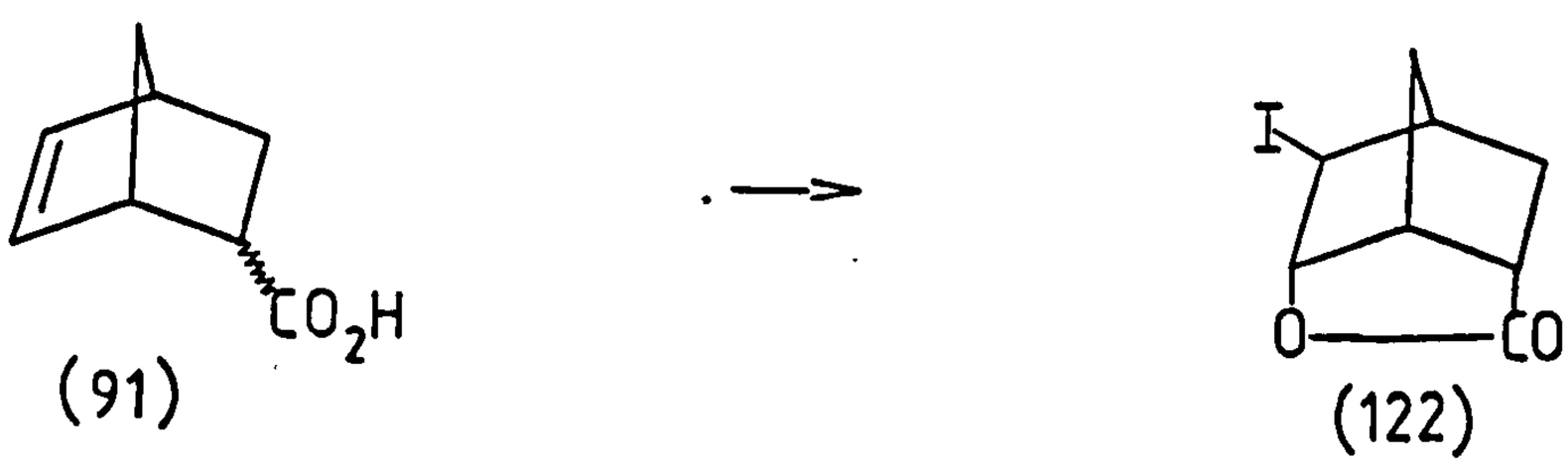
νmax cm^{-1} ($CHCl_3$) 3200 (m, COOH), 1710 (s, C = 0);
δ(60 MHz, $CDCl_3$) 11.0 (s, H-10), 6.08 (m, H-5, H-6), 2.78 (m, H-1, H-4), 2.35 (t, H-9), 1.95-0.9 (m, H-7a, H-7b,

H-3exo, H-2, H-8), 0.5 (2brd, H-3endo); J(Hz) (3-exo, 3-endo) 12; $M^{+\cdot}$ 166, ($M^{+\cdot}$ - COOH) 121, ($M^{+\cdot}$ - COOH - C_2H_5) 92.

4.2.2.26. General method for the iodolactonisation of unsaturated acids.

To the stirred solution of unsaturated acid (10 mmole) in 0.5 N aqueous sodium hydrogen carbonate (60 ml) cooled in an ice-bath, a solution of iodine (10 mmole) and potassium iodide (60 mmole) in water (32 ml) was added. The reaction was carried out with protection from light, by the method of van Tamelen and Shamma;[5] after 0.5 h the ice-bath was removed and the mixture stirred for 1 h before being kept at room temperature for 16 h. The product was extracted with chloroform (6 x 30 ml), the combined chloroform extracts washed with 1 M aqueous sodium thiosulphate (60 ml), 0.1 N aqueous sodium hydrogen carbonate (2 x 40 ml), water (2 x 40 ml), dried ($MgSO_4$) and the solvent evaporated to afford the iodolactone.

4.2.2.27. 6-endo-Hydroxy-5-exo-iodonorborn-2-endo-ylcarboxylic acid γ-lactone (122).—

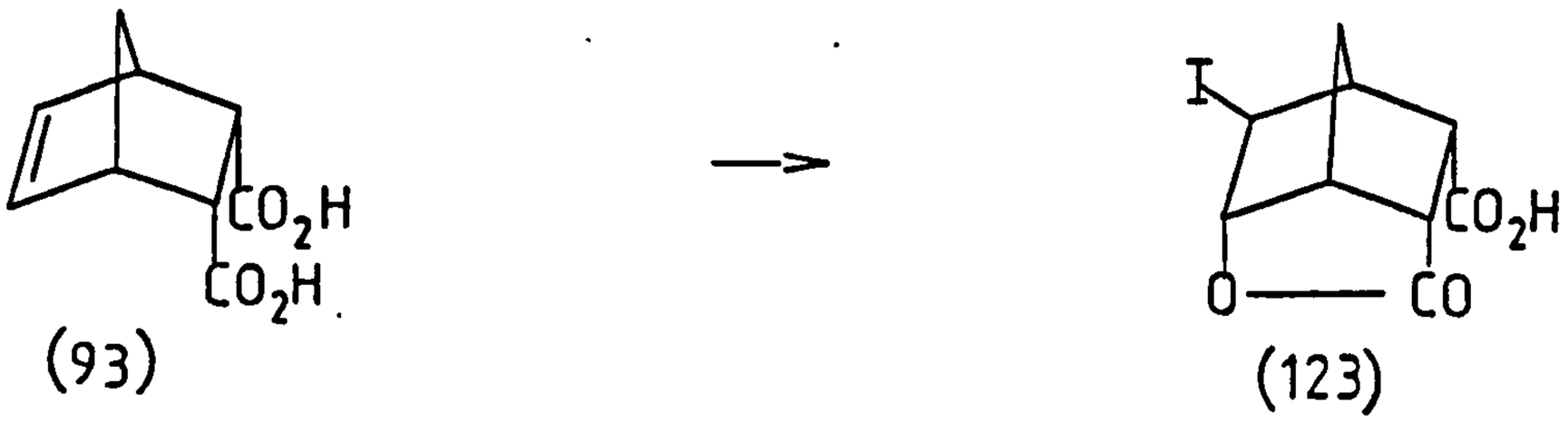


(91) (122)

The acid (91) (18.0 g, 0.13 mole) in 0.5 N aqueous sodium hydrogen carbonate (780 ml) and a solution of iodine (33.1 g, 0.13 mole) and potassium iodide (127.7 g, 0.8 mole) in water (400 ml) were mixed and the

reaction carried out as in 4.2.2.26. to give the γ-iodolactone (122) (20.8 g, 0.08 mole, 60.4%) as a white crystalline solid (light petroleum b.p. 60-80° -ethyl acetate) m.p. 57-59°. (Lit.[116] m.p. 58-59°).

4.2.2.28. 6-endo-Hydroxy-5-exo-iodo-3-endo-carboxynorborn-2-endo-ylcarboxylic acid γ-lactone (123).-



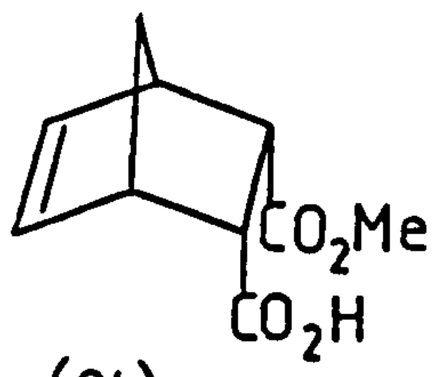
(93) (123)

The acid (93) (6.90 g, 0.04 mole) in 0.5 N aqueous sodium bicarbonate (230 ml) and a solution of iodine (9.6 g, 0.04 mole) and potassium iodide (48.9 g, 0.3 mole) in water (114 ml) were mixed and allowed to react as in 4.2.2.26. After completion of reaction the mixture was acidified and extracted with chloroform (7 x 100 ml), the chloroform extracts were washed with 1 M sodium thiosulphate (2 x 100), water (2 x 100 ml), dried ($MgSO_4$) and the solvent evaporated to afford 6-endo-hydroxy-5-exo-iodo-3-endo-carboxynorborn-2-endo-ylcarboxylic acid γ-lactone (123) (6.20 g, 0.02 mole, 53%) as a white crystalline solid (ethyl acetate) m.p. 146-148°.

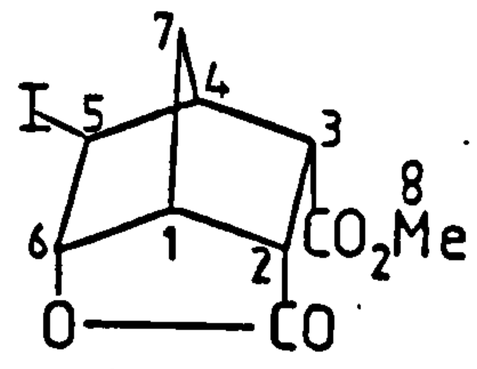
νmax cm^{-1} (Nujol) 3200 (br, COOH), 1800 (s, C = O of a γ-lactone), 1710 (s, C = O of acid); δ(60 MHz, Methanol-d_4) 5.18 (d, H-6exo), 4.60 (d, H-5endo), 3.28 (m, H-1), 3.17 (q, H-3exo), 2.89 (m, H-4), 2.80 (q, H-2exo), 2.44 (brd, H-7syn), 1.91 (brd, H-7anti); J(Hz)

(1,6-exo) 6, (5-endo, 7-anti) 3, (3-exo, 4) 4, (3-exo, 2-exo) 7, (1,2-exo) 4, (7-anti, 7-syn) 12; $M^{+\cdot}$ 308, ($M^{+\cdot}$ - I) 181.

4.2.2.29. 6-endo-Hydroxy-5-exo-iodo-3-endo-carbomethoxy-norborn-2-endo-ylcarboxylic acid γ-lactone (124).—



(94)



(124)

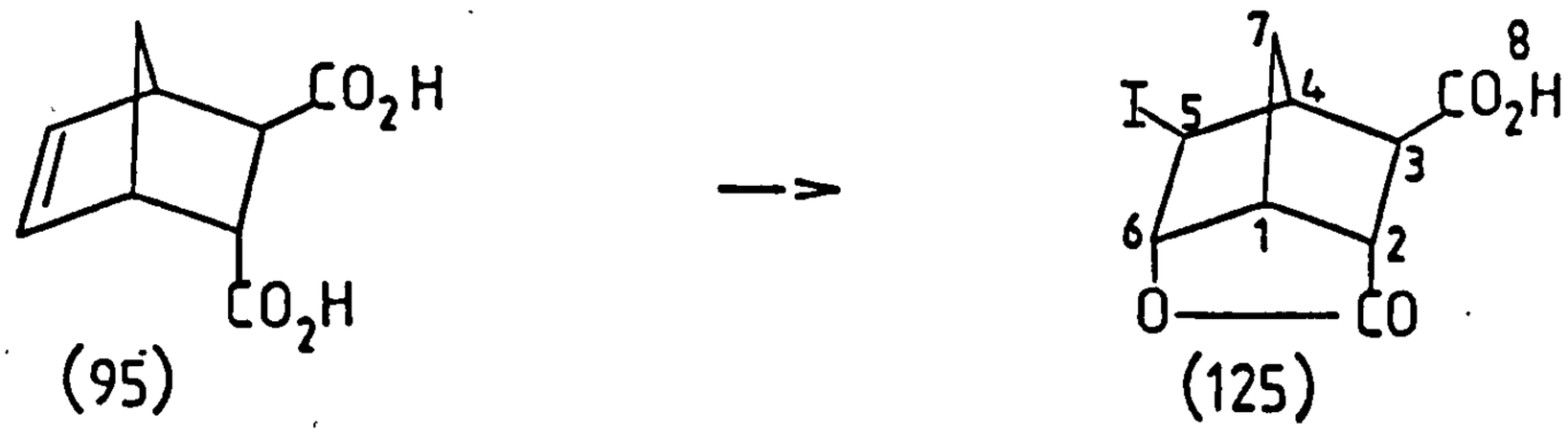
The solution of acid (94) (35.0 g, 0.18 mole) in 0.5 N sodium hydrogen carbornate (300 ml) and a solution of iodine (46.3 g, 0.18 mole) and potassium iodine (179.3 g, 1.08 mole) in water (450 ml) were mixed and the reaction carried out as in 4.2.2.26. to give 6-endo-hydroxy-5-exo-iodo-3-endo-carbomethoxynorborn-2-endo-ylcarboxylic acid γ-lactone (124), (43.79 g, 0.136 mole, 76.16%) as a white crystalline solid m.p. 98-99° (benzene-light petroleum b.p. 60-80°). (Lit.[120] m.p. 97-98°).

νmax cm^{-1} (Nujol) 1785 (s, C = O of γ-lactone) 1730 (s, C = O of ester);

δ(90 MHz, $CDCl_3$) 5.18 (d, H-6exo), 4.62 (d, H-5endo), 3.72 (s, H-8), 3.31 (m, H-1), 3.11 (q, H-3exo), 2.89 (m, H-4), 2.30 (q, H-2exo), 2.44 (dxt, H-7syn), 1.89 (dxq, H-7anti), J(Hz) (6-exo, 1) 6, (5, 7-anti) 3, (2-exo, 1) 6, (2-exo, 3) 4, (7-anti, 7-syn) 12;

$M^{+\cdot}$ 322, ($M^{+\cdot}$ - CH_3) 307, ($M^{+\cdot}$ - I) 195.

4.2.2.30. 6-endo-Hydroxy-5-exo-iodo-3-exo-carboxynorborn-2-endo-ylcarboxylic acid γ-lactone (125).-



A solution of the acid (95) (6.0 g, 0.03 mole) in 0.5 N sodium hydrogen carbornate (396 ml), and a solution of iodine (8.4 g, 0.03 mole) and potassium iodide (30.0 g, 0.18 mole) in water (100 ml) were mixed and allowed to react as in 4.2.2.26. Work up of the reaction as in 4.2.2.28. gave 6-endo-hydroxy-5-exo-iodo-3-exo-carboxynorn-2-endo-ylcarboxylic acid γ-lactone (125) (7.40 g, 0.03 mole, 72.9%) as a white crystalline solid (ethyl acetate) m.p. 127-129°. (Lit.[121] m.p. 126°).

νmax cm^{-1} (Nujol) 3200 (br, COOH), 1760 (s, C = O of γ-lactone), 1710 (s, C = O of acid).

δ(90 MHz, Methanol-d_4) 5.18 (s, H-8), 5.10 (d, H-6exo), 4.05 (d, H-5endo), 3.24 (m, H-1), 2.99 (m, H-2exo, H-3endo), 2.92 (brs, H-4), 2.32 (q, H-7syn), 1.89 (brd, H-7anti); J(Hz) (6-exo, 1) 4, (5-endo, 7-anti) 2, (7-anti, 7-syn) 12; $M^{+\cdot}$ 308, ($M^{+\cdot}$ - I) 181.

4.2.2.31. 6-endo-Hydroxy-5-exo-iodo-3-exo-carbomethoxynorborn-2-endo-ylcarboxylic acid γ-lactone (126).-

(125) (126)

A solution of the γ-iodolactone acid (125) (1.0 g, 3.24 mmole) in ether (65 ml) was cooled in an ice-bath and methylated with diazomethane as in 4.1.1.11, to afford 6-endo-hydroxy-5-exo-iodo-3-exo-carbomethxynorborn-2-endo-ylcarboxylic acid γ-lactone (126) (0.95 g, 2.95 mmole, 91.3%) as a white crystalline solid (ethyl acetate) m.p. 100-101°. (Lit.[121] m.p. 99°).

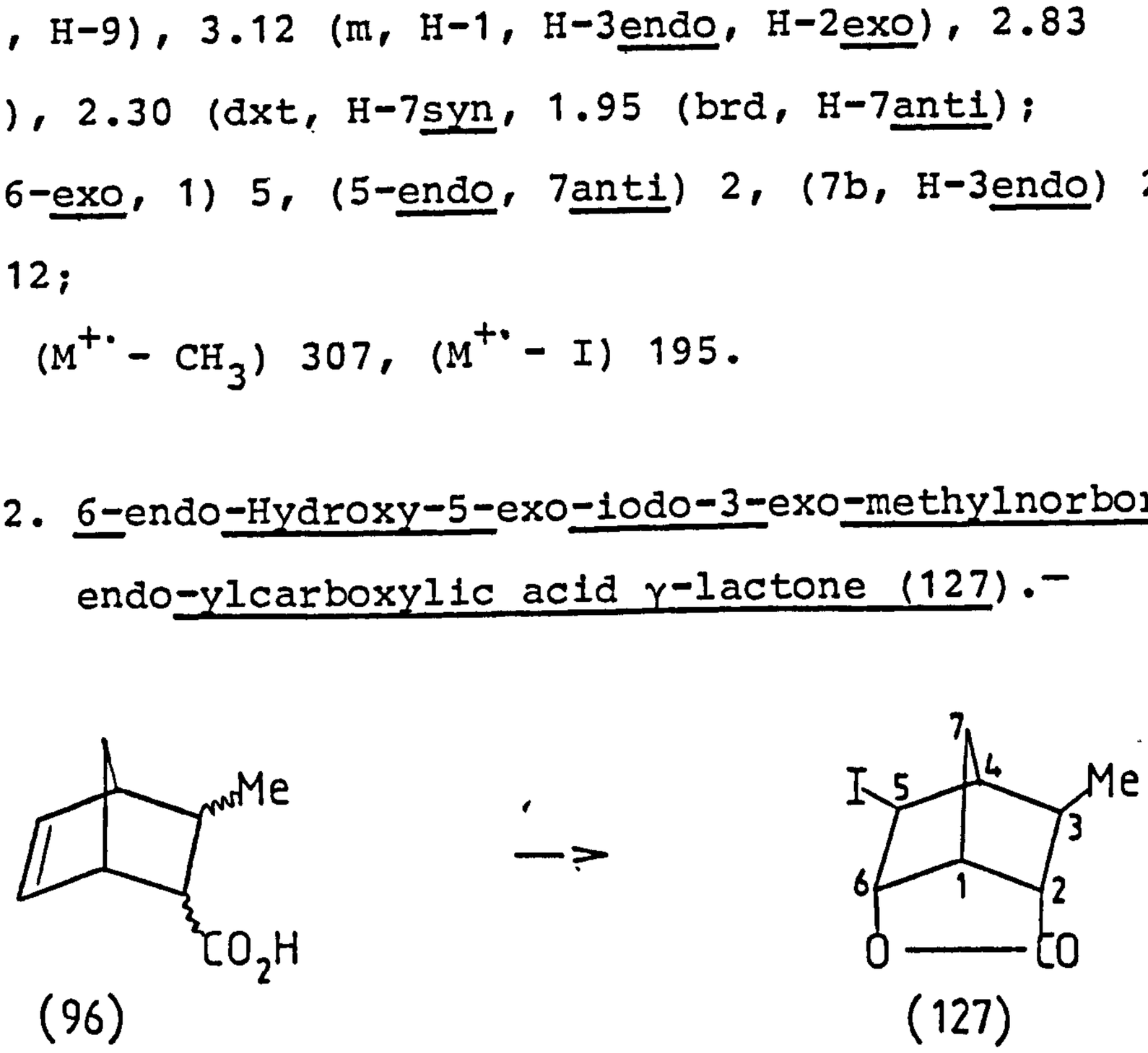
νmax cm^{-1} ($CHCl_3$) 1760 (s, C = O of γ-lactone), 1735 (s, C = O of ester);

δ(60 MHz, $CDCl_3$) 5.10 (d, H-6exo), 3.88 (d, H-5endo), 3.71 (s, H-9), 3.12 (m, H-1, H-3endo, H-2exo), 2.83 (m, H-4), 2.30 (dxt, H-7syn, 1.95 (brd, H-7anti);

J(Hz) (6-exo, 1) 5, (5-endo, 7anti) 2, (7b, H-3endo) 2, (7-anti, 7-syn) 12;

$M^{+\cdot}$ 322, ($M^{+\cdot}$ - CH_3) 307, ($M^{+\cdot}$ - I) 195.

4.2.2.32. 6-endo-Hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylcarboxylic acid γ-lactone (127).-



(96) (127)

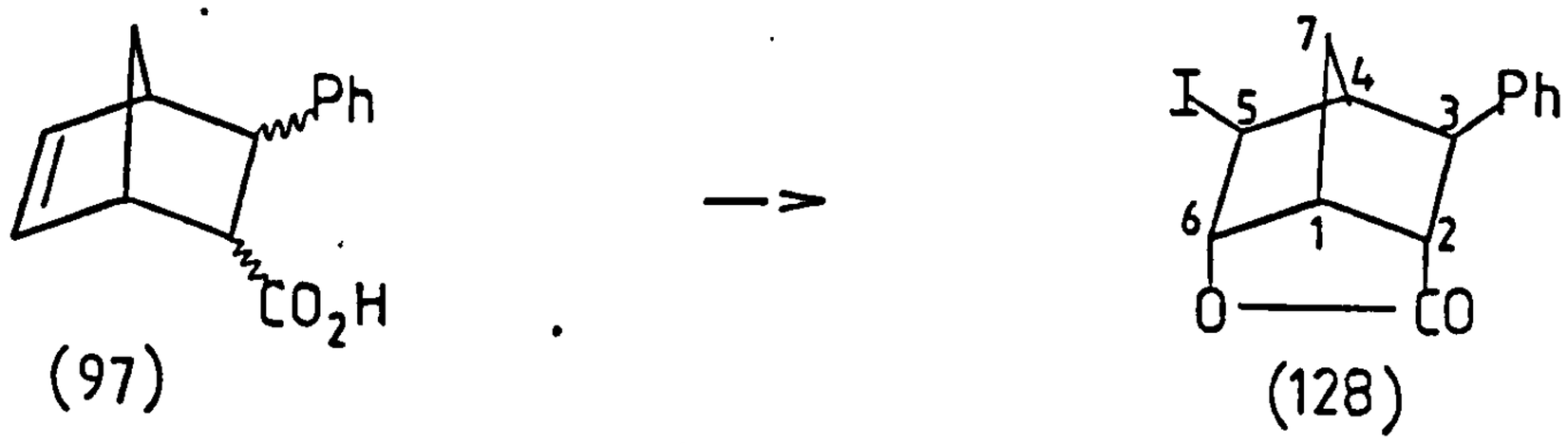
The solution of acid (96) (a mixture of trans-endo carboxyl and trans-exo carboxyl isomers) (11.0 g, 0.07 mole) in 0.5 N aqueous sodium hydrogen carbornate (453 ml), and a solution of iodine (18.5 g, 0.07 mole) and potassium iodide (71.9 g, 0.43 mole) in water (227 ml) were allowed to react as in 4.2.2.26, to give 6-endo-hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylcarboxylic acid γ-lactone (127) (15.80 g, 0.06 mole, 78.56%) as a white crystalline solid, m.p. 52-54°. (Lit.[102] m.p. 54-55°).

νmax cm^{-1} ($CHCl_3$) 1760 (s, C = O);

δ(60 MHz, $CDCl_3$) 5.10 (d, H-6exo), 3.85 (d, H-5endo), 3.10 (t, H-1), 2.42 (brs, H-4), 2.30 (m, H-7syn), 2.12 (m, H-7anti), 2.12 (m, H-3endo), 2.10 (m, H-2exo) and 1.10 (d, CH_3). J(Hz) (6-exo, 1) 6; (5-endo, 7-anti) 3, (1,2-exo) 6, (CH_3, 3-endo) 7;

$M^{+\cdot}$ 278, ($M^{+\cdot}$ - CH_3) 263, ($M^{+\cdot}$ - I) 151.

4.2.2.33. 6-endo-Hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo-ylcarboxylic acid γ-lactone (128).-

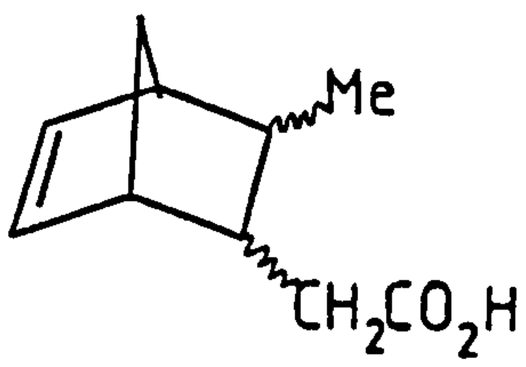


The solution of acid (97) (a mixture of trans-endo carboxyl and trans-exo carboxyl isomers) (4.32 g, 0.02 mole) in 0.5 N aqueous sodium hydrogen carbornate (130 ml), and a solution of iodine (5.1 g, 0.02 mole) and potassium iodide (19.9 g, 0.12 mole) in water (100 ml) were mixed and allowed

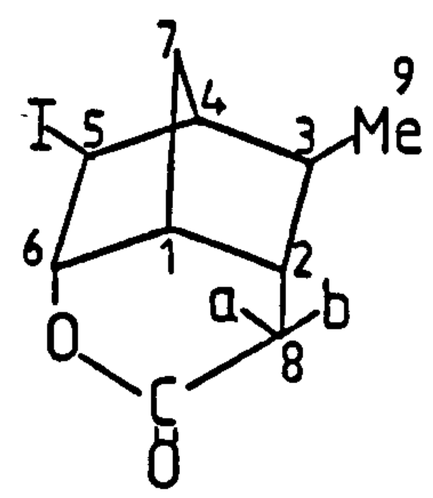
to react as in 4.2.2.26 to afford 6-endo-hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo-ylcarboxylic acid γ-lactone (128) (5.40 g, 0.016 mole, 79.4%) as a white crystalline solid (ethyl acetate) m.p. 124-126.5°. (Lit.[97] m.p. 126-126.5°).

νmax cm^{-1} ($CHCl_3$) 1765 (s, C = O), 1600 (m, aromatic);
δ(60 MHz, $CDCl_3$) 7.20 (m, C_6H_5), 5.20 (d, H-6exo), 4.04 (d, H-5endo), 3.30 (m, H-1, H-4), 2.90 (m, H-2exo, H-3endo), 2.20 (m, H-7anti, H-syn);
$J(H_z)$ (6-exo, 1) 6, (5-endo, 7-anti)3;
$M^{+\cdot}$ 340, $(M^{+\cdot} - C_6H_5)$ 263, $(M^{+\cdot} - I)$ 213.

4.2.2.34. 6-endo-Hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylacetic acid δ-lactone (133).—



(100)



(133)

The solution of acid (100) (a mixture of trans-endo carboxyl and trans-exo carboxyl isomers) (2.54 g, 0.015 mole) in 0.5 N aqueous sodium hydrogen carbornate (110 ml), and a solution of iodine (3.90 g, 0.015 mole) and potassium iodide (15.2 g, 0.09 mole) in water (55 ml) were mixed and allowed to react as in 4.2.2.26. to give 6-endo-hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylacetic acid δ-lactone (133) (2,30 g, 7.8 mmole, 52.5%), as a white crystalline

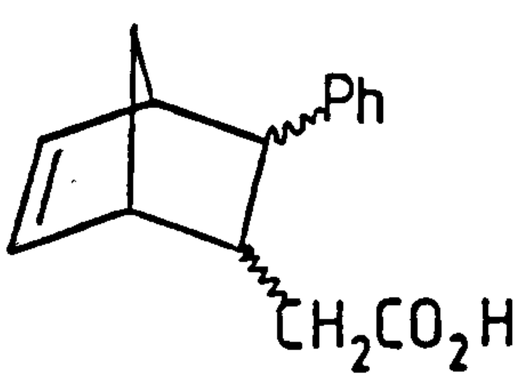
solid (CCl_4) m.p. 97-99°.

Found: C, 41.06, H, 4.45. $C_{10}H_{13}O_2$ requires C, 41.09, H, 4.45%;

νmax cm^{-1} ($CHCl_3$) 1730 (s, C = O);

δ(90 MHz, C_6D_6) 4.97 (brt, H-6exo), 3.54 (q, H-5endo), 2.12 (dxq, H-8a, H-8b), 1.71 (m, H-1, H-4, H-2exo), 1.27 (m, H-7syn), 1.13 (m, H-7anti), 0.79 (m, H-3endo), 0.52 (d, H-9); J(Hz) (8a, 8b), 18, (8a, 2-exo) 3, (8b, 2-exo) 5, (5-endo, 7-anti) 3.2, (5-endo, 6-exo) 2, (6-exo, 1) 4, (9, H-3endo) 6; $M^{+\cdot}$ 292, ($M^{+\cdot}$ - CH_3) 277, ($M^{+\cdot}$ - CO) 264, ($M^{+\cdot}$ - I) 165.

4.2.2.35. 6-endo-Hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo-ylacetic acid δ-lactone (134).—



(105)

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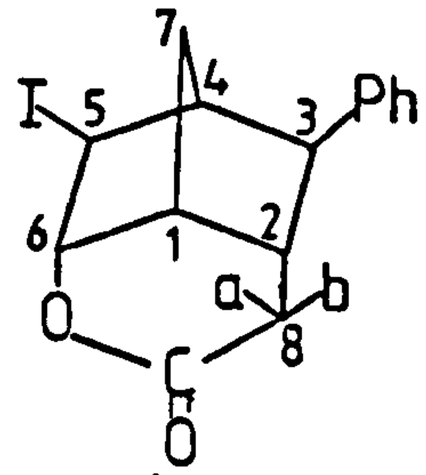


(134)

The solution of acid (105) (a mixture of trans-exo carboxyl and trans-endo carboxyl isomers) (2.0 g, 9.77 mmole) in aqueous 0.5 N sodium hydrogen carbornate (53 ml), and a solution of iodine (2.25 g, 8.86 mmole) and potassium iodide (8.75 g, 52.72 mmole) in water (28 ml) were mixed and allowed to react as in 4.2.2.26. to give 6-endo-hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo-ylacetic acid δ-lactone (134) (2.20 g, 6.21 mmole, 70.96%) as a white crystalline solid (light petroleum b.p. 60-80°-

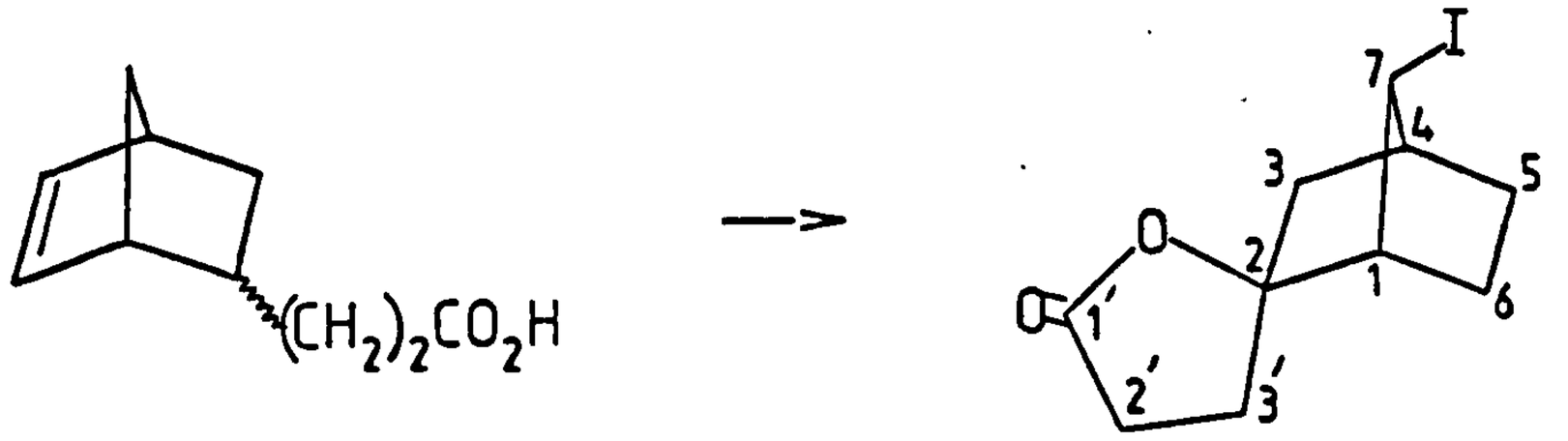
ethyl acetate), m.p. 108-110°. Found: C, 50.89, H, 4.46, I, 35.56. $C_{15}H_{15}IO_2$ requires C, 50.84, H, 4.23, I, 35.87%.

νmax cm^{-1} ($CHCl_3$) 1735 (s, C = O), 1600 (m, aromatic); δ(90 MHz, $CDCl_3$) 7.23 (m, C_6H_5), 5.33 (d, H-6exo), 4.0 (t, H-5endo), 2.73 (m, H-3endo, H-8a, H-8b), 2.53 (brd, H-4, H-1, H-2exo), 2.23 (m, H-7anti, H-7syn);

J(Hz) (6-exo, 1) 5, (5-endo, 7-anti), (5-endo, 6-exo) 2, (8, 2-exo) 3;

$M^{+\cdot}$ 354, ($M^{+\cdot}$ - I) 227, ($M^{+\cdot}$ - I - CO_2) 183

4.2.2.36. 3'-(2-exo-Hydroxy-7-anti-iodonorbornan-2-endo-yl) propionic acid spiro-γ-lactone (135).-



(121) (135)

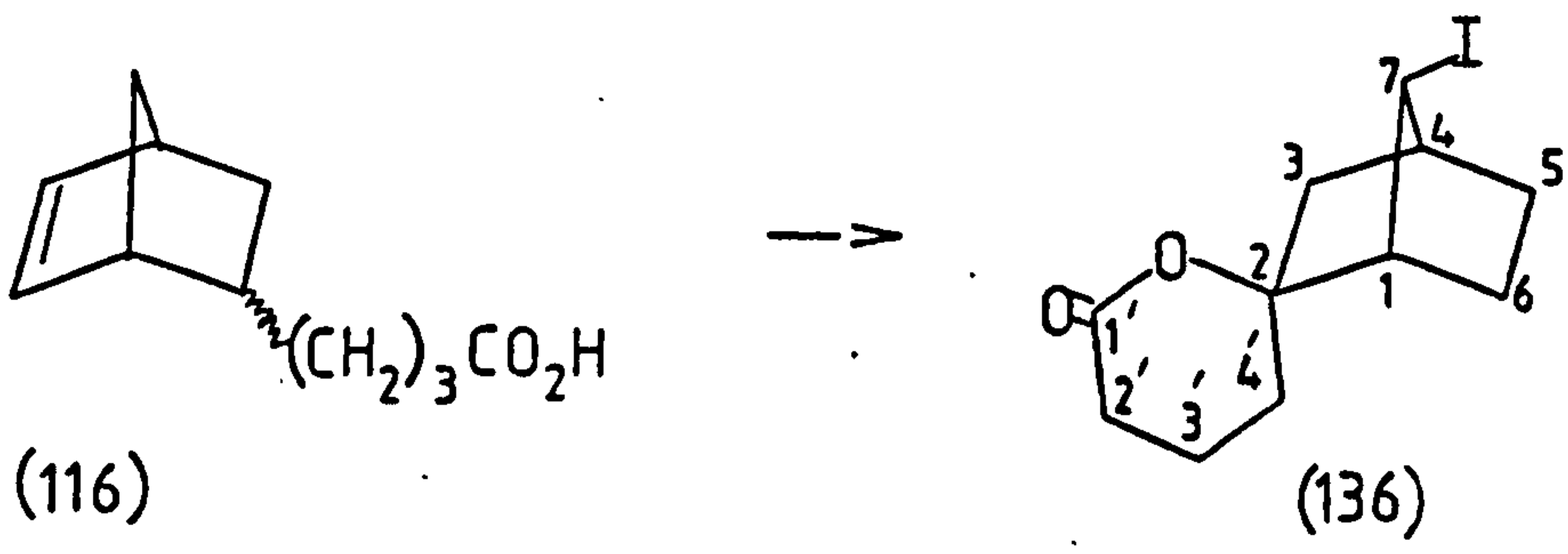
The solution of acid (121) (a mixture of endo and exo isomers) (1.0 g, 6mmole) in 0.5 N aqueous sodium hydrogen carbornate (45 ml), and a solution of iodine (1.53 g, 6 mmole) and potassium iodide (6.0 g, 36.1 mmole) in water (14 ml) were mixed and allowed to react as in 4.2.2.26. The product as a yellow oil was purified by p.l.c. [2:5 ethyl acetate/light petroleum b.p. 60-80°, 60 x 20 x 0.1 cm silica gel plate] to afford 3-(2-exo-7-hydroxy-7-anti-iodonorborn-2-endo-yl) propionic acid spiro γ-lactone (135) (0.40 g, 1.37 mmole) as a white crystalline

solid (ethyl acetate/light petroleum b.p. 60-80°) m.p. 91-93°, R_F = 0.7. (Lit.[93] m.p. 92.5-96.5°).

νmax cm^{-1} ($CHCl_3$) 1770 (s, C = O);

δ(90 MHz, $CDCl_3$) 3.95 (brs, H-7syn), 2.6-1.40 (overlapping m, H-1, H-2-exo, H-2-endo; H-3-exo, H-3-endo, H-4, H-5exo, H-5endo, H-2' and H-3'); $M^{+\cdot}$ 292, ($M^{+\cdot}$ - I) 165

4.2.2.37. 4'-(2-exo-Hydroxy-7-anti-iodonorborn-2-endo-yl) butyric acid spiro-δ-lactone (136).-



(116) (136)

The acid (116) (a mixture of endo and exo isomers) (1.41 g, 7.8 mmole) in 0.5 N aqueous sodium hydrogen carbornate (47 ml), and a solution of iodine (1.98 g, 7.8 mmole) and potassium iodine (78 g, 47 mmole) in water were mixed and allowed to react as in 4.2.2.26. Extraction of the reaction mixture did not give any neutral product of iodolactone. The remaining alkaline reaction mixture was acidified and extracted with chloroform (4 x 40 ml), the combined chloroform extracts were washed with water (50 ml), dried ($MgSO_4$) and the solvent evaporated to give another yellow oil (0.8 g). This oil was purified by p.l.c. [60 x 20 x 0.1 cm silica gel plate ($CHCl_3$)] to afford 4'-(2-exo-Hydroxy-7-anti-iodonorborn-2-endo-yl)

<u>butyric acid spiro-δ-lactone</u> (136) (0.48 g, 1.57 mmole, 20%) as a white crystalline solid (ethyl acetate/light petroleum b.p. 60-80°) m.p. 94.5-96°.

Found: C, 42.90; H, 5.02; I, 41.69. $C_{11}H_{15}O_2I$ requires C, 43.14; H, 4.90; I, 41.50%.

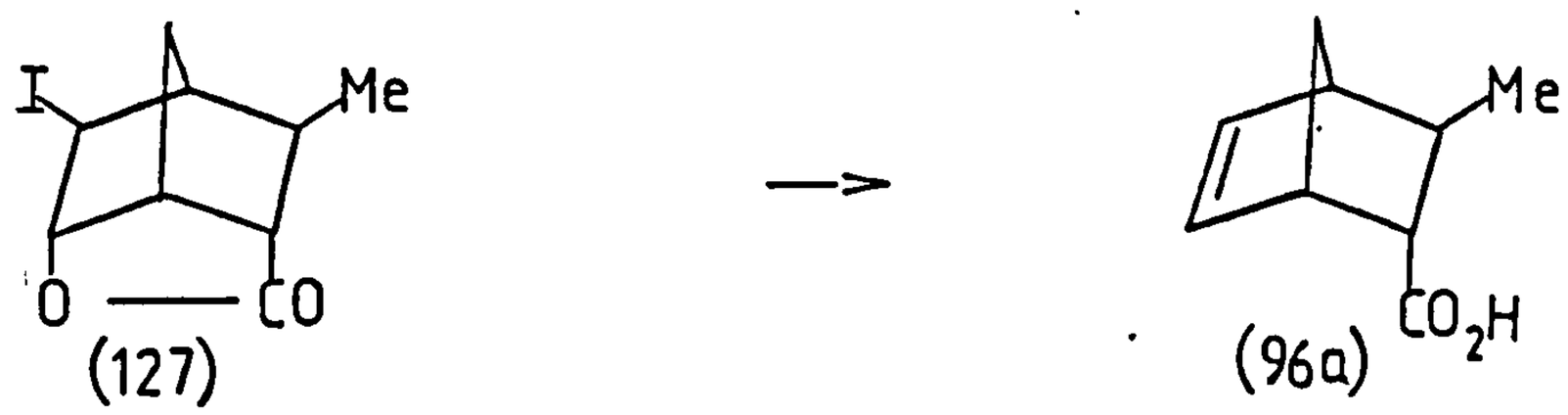
νmax cm^{-1} ($CHCl_3$) 1735 (s, C = O);

δ(90 MHz, $CDCl_3$) 4.47 (brs, H-7<u>syn</u>), 2.44 (m, H-1, H-4, H-3<u>exo</u>, H-2'), 1.97 (m, H-3', H-4', H-3<u>endo</u>, H-5<u>exo</u>), 1.64 (m, H-6<u>exo</u>), 1.44 (m, H-5<u>endo</u>), 1.22 (m, H-6<u>endo</u>);

δ(^{13}C, $CDCl_3$) 170.4 (s, C-1'), 88.30 (s, C-2), 54.30 (d, C-1), 44.70 (d, C-4), 43.90 (t, C-3), 32.07 (t, C-2'), 29.08 (t, C-4'), 26.91 (t, C-5), 30.14 (d, C-7), 21.93 (t, C-6), 17.0 (t, C-3');

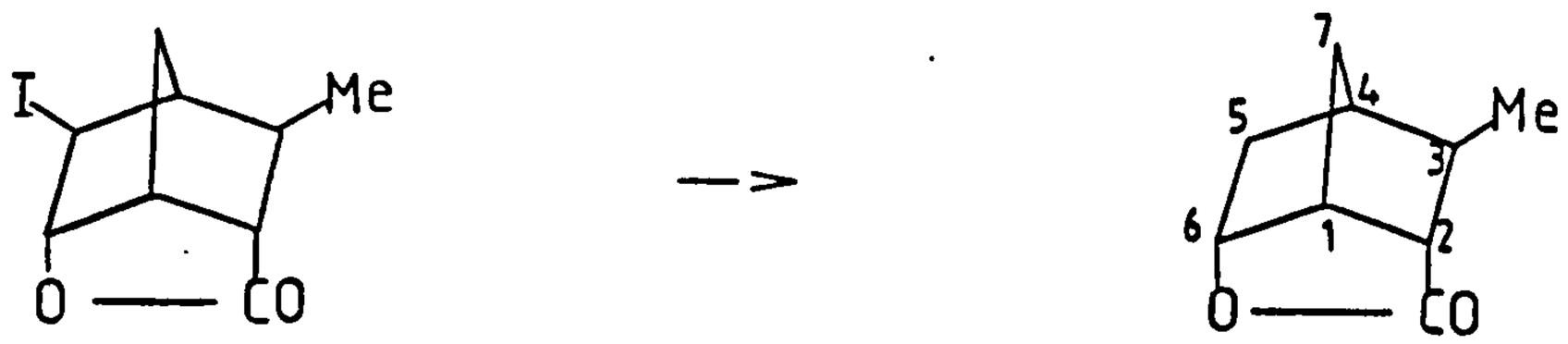
$M^{+\cdot}$ 306, ($M^{+\cdot}$ - CO) 278, ($M^{+\cdot}$ - C_3H_6O) 2.08, ($M^{+\cdot}$ - I) 179.

4.2.2.38. <u>3-exo-Methylnorborn-5-en-2-endo-ylcarboxylic acid (96a)</u>.-



The acid (96a) was prepared from the γ-iodolactone (127) (3.10 g, 11.15 mole) in acetic acid (7 ml) and zinc powder (2.7 g) by the method of Berson and Ben-Efraim;[129] yield (1.42 g, 9.3 mmole, 74.3%) as a white crystalline solid (carbon tetrachloride) m.p. 95-97°. (Lit.[102] m.p. 96°).

4.2.2.39. 6-endo-Hydroxy-3-exo-methylnorborn-2-endo-ylcarboxylic acid γ-lactone (146a).—



(127) (146a)

The γ-lactone (146a) was prepared from the γ-iodolactone (127) (1.39 g, 5 mmole), tri-n-butyltin chloride (0.325 g, 1 mmole) and sodium borohydride (0.236 g, 6.3 mmole) in ethanol (180 ml), by the method of Corey and Suggs;[131] yield (0.4 g, 2.6 mmole, 55%) as a white crystalline solid (ethyl acetate/light petroleum b.p. 60-80°) m.p. 70-72°. (Lit.[95] m.p. 70-71°).

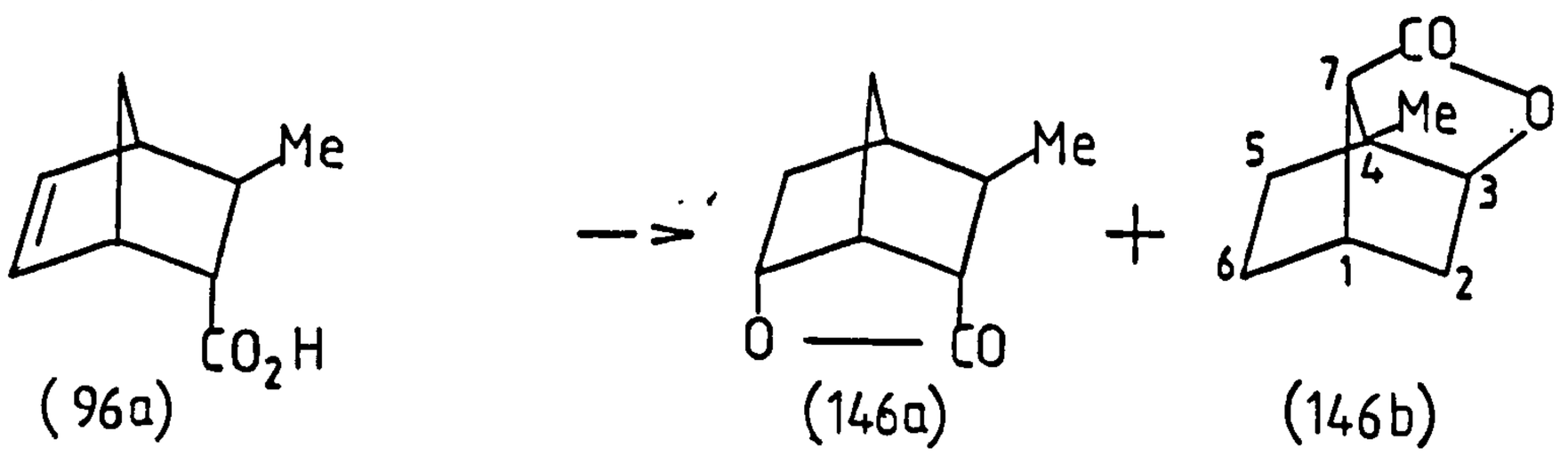
νmax cm^{-1} ($CHCl_3$) 1765, (s, C = O);

δ(60 MHz, $CDCl_3$) 4.75 (t, H-6exo), 3.10 (t, H-1), 2.10 (m, H-2exo, H-4), 1.9-1.25 (m, H-5, H-7anti, H-7syn, H-3endo), 1.10 (d, CH_3);

J)Hz) (6-exo, 1) 6, (6-exo, 5-exo) 6, (1,2-exo) 6, (CH_3, 3-endo) 7;

$M^{+\cdot}$ 151, ($M^{+\cdot}$ - CH_3) 136, ($M^{+\cdot}$ - CH_3 - CO) 108.

4.2.2.40. Reaction of 3-exo-Methylnorborn-5-en-2-endo-ylcarboxylic acid (96a) with Sulphuric Acid.—



(96a) (146a) (146b)

A mixture of endo-acid (96a) (0.7 g, 4.6 mmole) and sulphuric acid[130] (50%, 10 ml) was stirred at room temperature for 22 h. The resultant brown homogenous solution was poured onto a mixture of ice (20 g) and water (80 ml), and the mixture extracted with ether (6 x 40 ml). The combined ether extracts were washed with 0.5 N sodium hydrogen carbornate (2 x 50 ml), water (2 x 50 ml), dried ($MgSO_4$) and the solvent evaporated to give a mixture of 6-endo-hydroxy-3-exo-methylnorborn-2-endo-ylcarboxylic acid γ-lactone (146a) and 3-exo-hydroxy-4-methylnorborn-7-anti-ylcarboxlic acid γ-lactone (146b), (0.5 g) as a yellow oil.

νmax cm^{-1} ($CHCl_3$) 1765 (s, C = O);

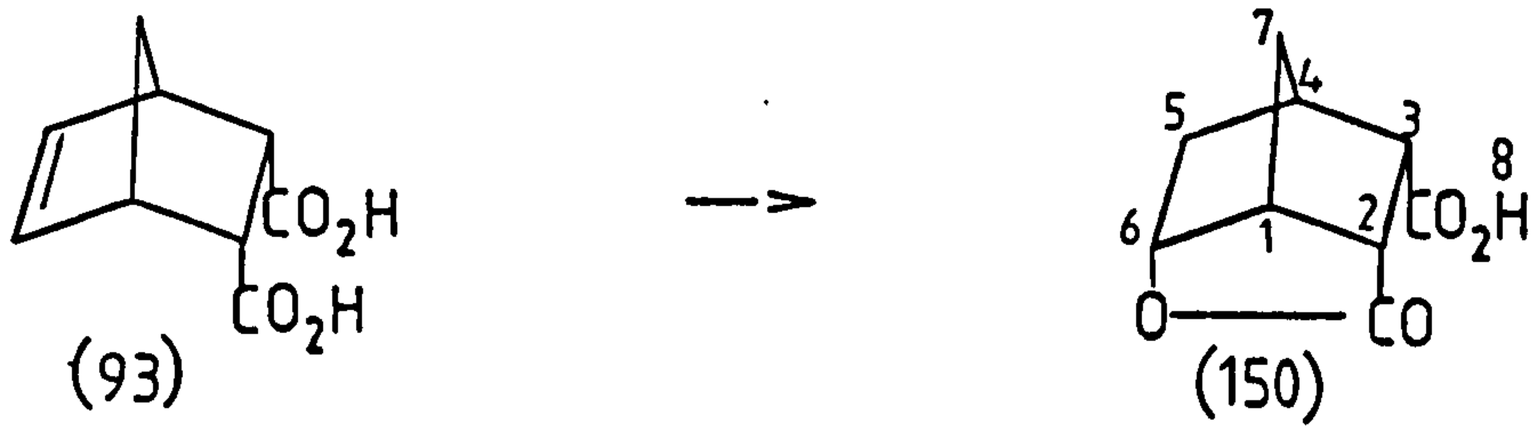
δ(60 MHz, $CDCl_3$) 4.75 (t, H-6exo), 3.15 (t, H-1), 1.10 (d, CH_3) of (146a) and 4.27 (brs, H-3endo), 1.26 (s, CH_3) of (146b);

Product proportions for the reaction, estimated by g.l.c. using Carbowax 20M on Chromosorb W 80-100 mesh at oven temperature 170°, are given below:

Lactone	%	Retention Time (Rt)
146a	47.88	7.4 min
146b	52.12	5.2 min

$M^{+\cdot}$ 152, ($M^{+\cdot}$ - CO) 128, ($M^{+\cdot}$ - CO - CH_3) 109.

4.2.2.41. 6-endo-Hydroxy-3-endo-carboxynorborn-2-endo-ylcarboxylic acid γ-lactone (150).-



A mixture of cis-acid (93) (4.0 g, 21.9 mmole) and concentrated sulphuric acid (20 ml) was stirred and gently heated at 60° for 1 h. The homogenous solution resulting was cooled to 0° in an ice-salt bath and small pieces of ice added until the volume reached 80 ml. The ice-salt bath was removed and the solution heated at 110° for 5 min, and cooled to afford precipitation of γ-lactone (150) (2.20 g, 12 mmole, 55.3%) as a white crystalline solid (ethyl acetate), m.p. 202-204°. (Lit.[99] m.p. 201°).

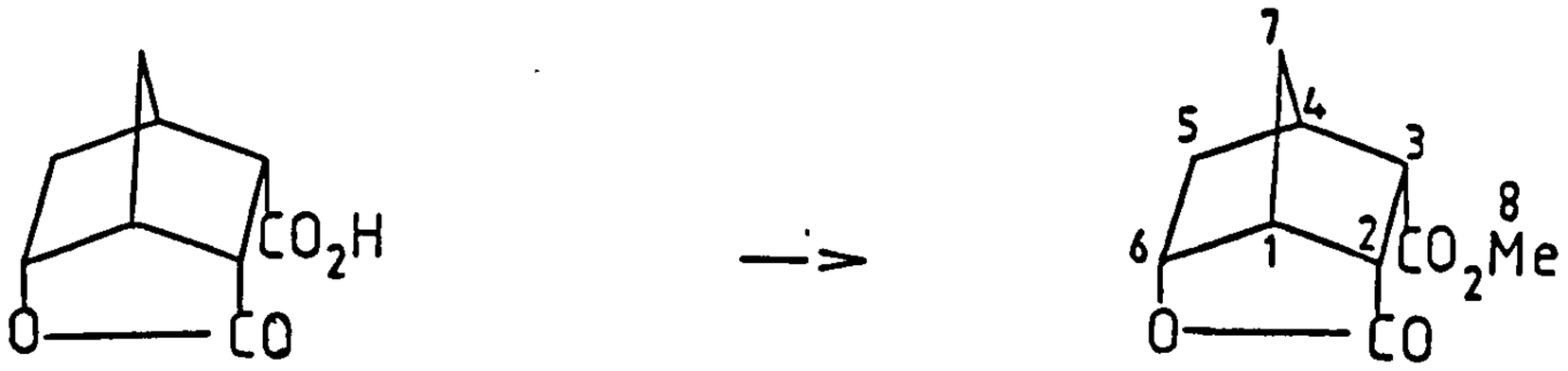
νmax cm^{-1} (Nujol) 3300 (br, COOH), 1760 (s, C = O) 1710 (s, C = O of acid);

δ(60 MHz, DMSO - d_6) 8.2 (s, H-8), 4.80 (t, H-6exo), 3.20 (t, H-1), 2.75 (brt, H-4), 2.7 (m, H-2exo, H-3exo), 1.90 (brd, H-5exo), 1.78 (m, H-7anti, H-7syn, H-5endo);

J(Hz) (6-exo, 1) 6, (6-exo, 5-exo) 6, (1,2-exo) 6, (7-anti, 7-syn) 12;

$M^{+\cdot}$ 182, ($M^{+\cdot}$ - CO) 154, ($M^{+\cdot}$ - 2CO) 116.

4.2.2.42. 6-endo-Hydroxy-3-endo-carbomethoxynorborn-2-endo-ylcarboxylic acid γ-lactone (152).-



(150) (152)

The solution of acid (150) (0.40 g, 2.2 mmole) in ether (50 ml) was methylated with diazomethane as in the method 4.1.1.11. to give 6-endo-hydroxy-3-endo-carbomethoxynorborn-2-endo-ylcarboxylic acid γ-lactone (152) (0.38 g, 1.9 mmole, 88.1%) as a white crystalline solid (ethyl acetate/light petroleum b.p. 60-80°), m.p. 81-83°. (Lit.[101] m.p. 82-83°).

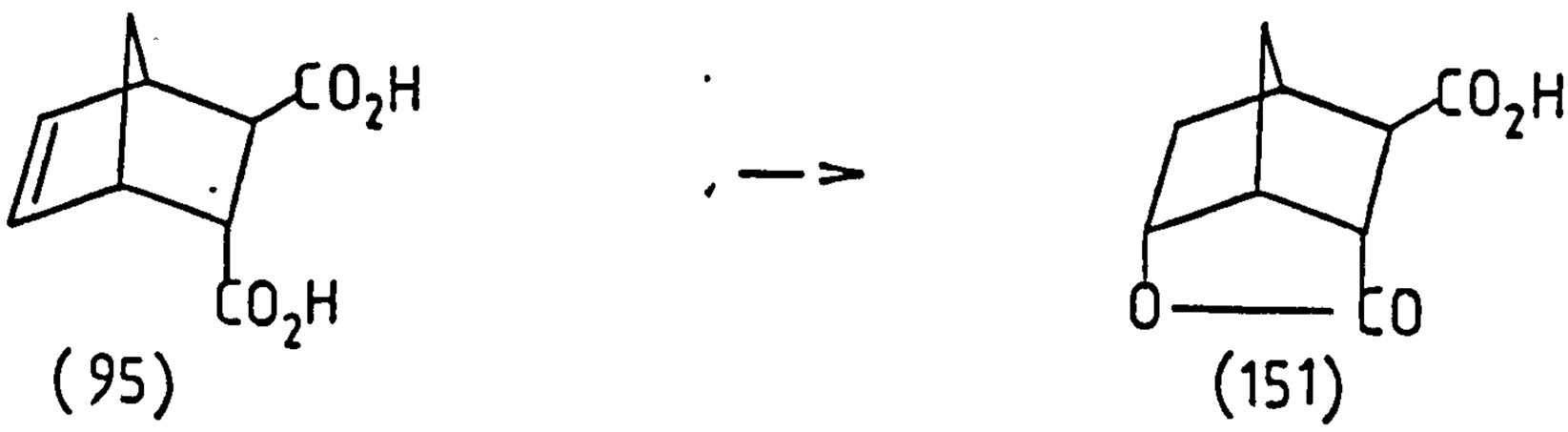
νmax cm^{-1} ($CHCl_3$) 1760 (s, C = O), 1735 (s, C = O of ester).

δ(60 MHz, $CDCl_3$) 4.8 (brt, H-6exo), 3.70 (s, H-8), 3.25 (m, H-1), 2.92 (m, H-4), 2.7 (m, H-2exo, H-3exo), 2.20 (brd, H-5exo), 1.80 (m, H-5-endo, H-7anti, H-7syn);

J(Hz) (5-exo, 1) 6, (6-exo, 5-exo) 6, (5-exo, 5-endo) 15;

$M^{+\cdot}$ 196, ($M^{+\cdot}$ - CH_3) 181, ($M^{+\cdot}$ - CO) 168.

4.2.2.43. 6-endo-Hydroxy-3-exo-carboxynorborn-2-endo-ylcarboxylic acid γ-lactone (151).-



(95) (151)

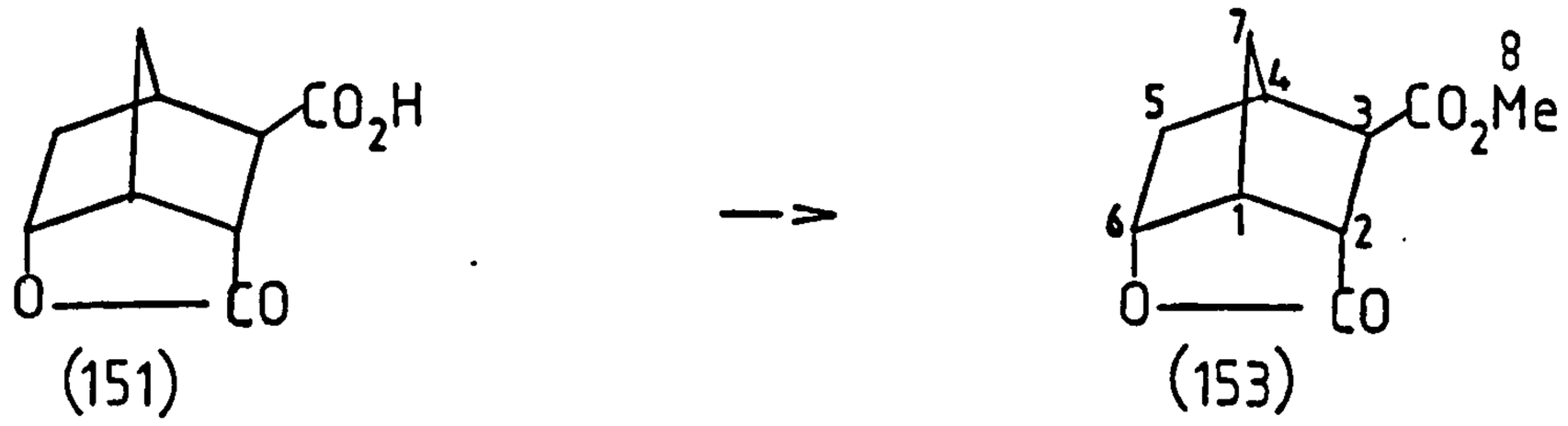
A mixture of trans-acid (95) (2.0 g, 10.9 mmole) and concentrated sulphuric acid (10 ml) was heated and allowed to react as in 4.2.2.41. to give 6-endo-hydroxy-3-exo-carboxynorborn-2-endo-ylcarboxylic acid γ-lactone (151) (1.2 g, 6.6 mmole, 63.5%) as a white crystalline solid (ethyl acetate), m.p. 133-135°. (Lit.[104] m.p. 133-134°).

νmax cm^{-1} (Nujol) 3300 (m, COOH), 1760 (s, C = O), 1720 (s, C = O);

δ(60 MHz, $CDCl_3$) 4.90 (t, H-6exo), 3.18 (m, H-1, H-4), 2.80 (m, H-2exo, H-3endo), 1.80 (m, H-5exo, H-5endo, H-7anti, H-7syn);

J(Hz) (6-exo, 1) 6, (6-exo, 5-exo) 6; $M^{+\cdot}$ 182.

4.2.2.44. 6-endo-Hydroxy-3-exo-carbomethoxynorborn-2-endo-ylcarboxylic acid γ-lactone (153).-



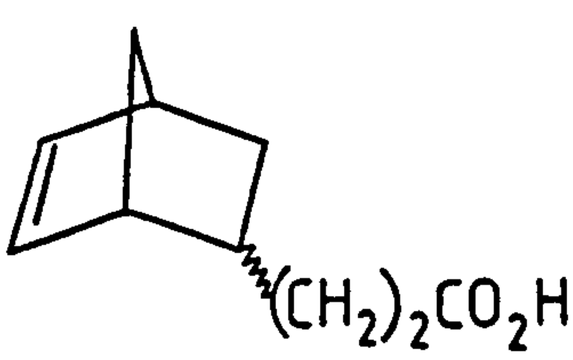
The solution of acid (151) (0.7 g, 3.8 mmole) in ether (70 ml) was methylated with diazomethane as in Method 4.1.1.11. to afford 6-endo-hydroxy-3-exo-carbomethoxynorborn-2-endo-ylcarboxylic acid γ-lactone (153) (0.73 g, 3.72 mmole, 97%) as a white crystalline solid, m.p. 77-78°.

νmax cm^{-1} ($CHCl_3$) 1760 (s, C = O), 1735 (s, C = O);

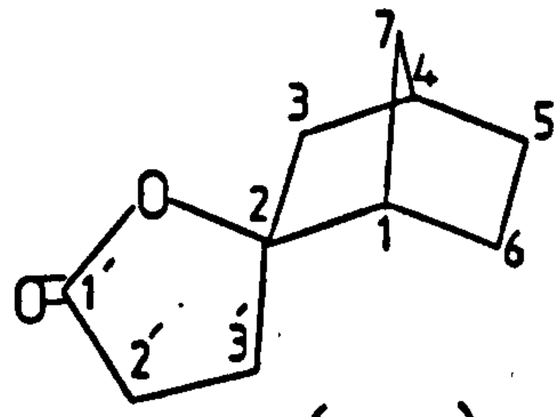
δ(60 MHz, $CDCl_3$) 4.80 (t, H-6exo), 3.73 (s, H-8), 3.20

(m, H-1, H-4), 2.75 (m, H-2exo, H-3endo), 1.70 (m, H-7anti, H-7syn, H-5exo and H-5endo); M^+ 196, ($M^+ - CH_3$) 181, ($M^{+\cdot} - CO$) 168.

4.2.2.45. 3'-(2-exo-Hydroxynorborn-2-endo-yl)propionic acid spiro-γ-lactone (148).-



(121)



(148)

The solution of acid (121) [a mixture of endo-acid (121a) and exo acid (121b)] (0.2 g, 1.2 mmole) in sulphuric acid (50%, 6 ml) was stirred at room temperature for 20 h. The resultant brown solution was worked up as in 4.2.2.40 to afford a yellow oil. The oil was distilled to give 3'-(2-exo-hydroxynorborn-2-endo-yl)propionic acid spiro-γ-lactone (148) (0.16 g, 0.96 mmole, 80%) as a colourless oil, b.p. 95° at 0.3 mm Hg.

Found: C, 72.18; H, 8.77. $C_{10}H_{14}O_2$ requires C, 72.29; H, 8.43%.

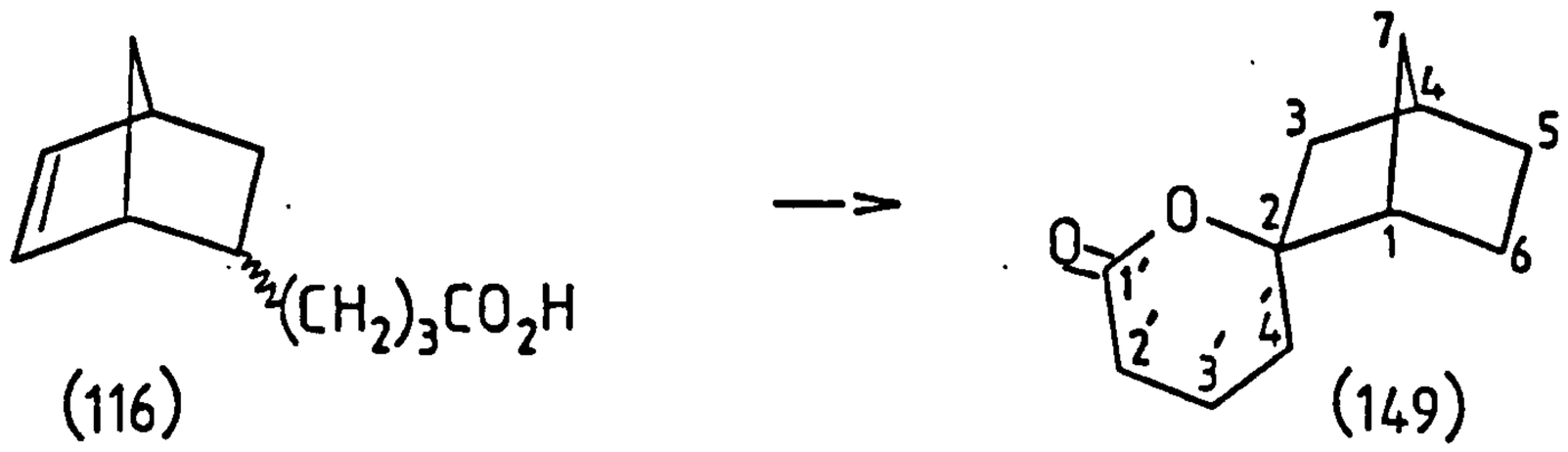
νmax cm^{-1} (CCl_4) 1780 (s, C = O);

δ(60 MHz, $CDCl_3$) 2.80-1.20 (overlapping m);

$\delta^{13}C$ ($CDCl_3$) 46.38 (d, C-1), 93.58 (s, C-2), 29.73 (t, C-3), 45.67 (d, C-4), 22.22 (t, C-5), 28.02 (t, C-6), 30.60 (t, C-7), 176.67 (s, C-1'), 36.40 (t, C-2'), 37.93 (t, C-3').

$M^{+\cdot}$ 166, ($M^{+\cdot} - C_2H_4$) 138, ($M^{+\cdot} - CO_2$) 124.

4.2.2.46. 4'-(2-exo-Hydroxynorborn-2-endo-yl)butyric acid spiro-δ-lactone (149).-



(116) (149)

The solution of acid (116) [a mixture of endo-acid (116a) and exo-acid (116b)] (0.2 g, 1.11 mmole) in sulphuric acid (50%, 6 ml) was stirred at room temperature for 20 h. The resultant brown solution was worked up as in 4.2.2.40. to give a yellow oil. The oil was distilled to afford 4'-(2-exo-hydroxynorborn-2-endo-yl)butyric acid spiro-δ-lactone (149) (0.15 g, 0.83 mmole, 78.9%) as a colourless oil, b.p. 100° at 0.3 mm Hg.

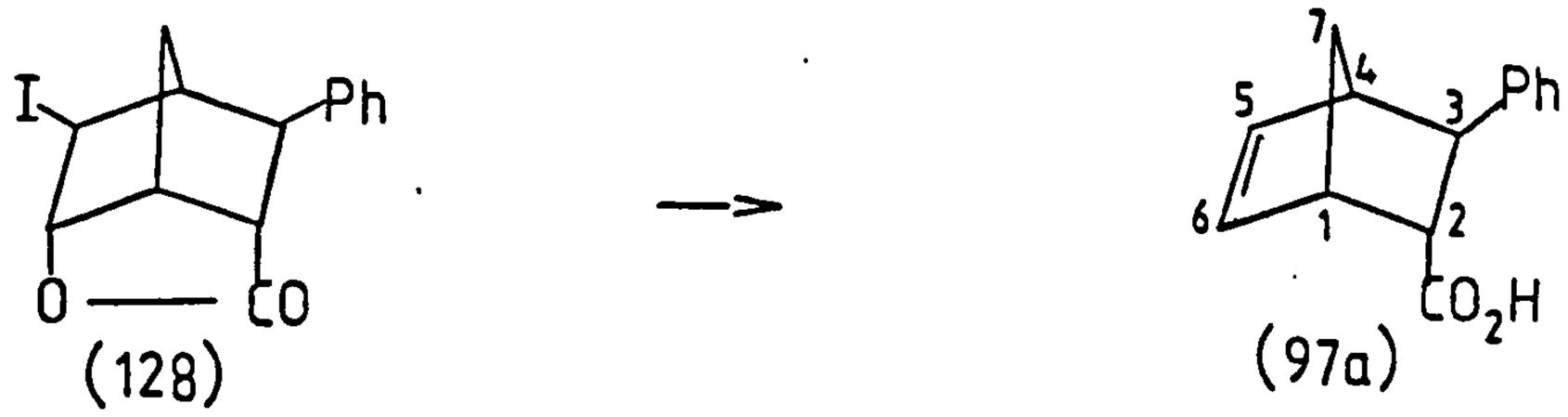
Found: C, 73.84; H, 9.04. $C_{11}H_{16}O_2$ requires C, 73.33; H, 8.89%.

νmax cm^{-1} (CCl_4) 1730 (s, C = O);

$\delta^{13}C$ ($CDCl_3$) 46.85 (d, C-1), 91.30 (s, C-2), 27.85 (t, C-3), 46.73 (d, C-4), 17.30 (t, C-5), 22.98 (t, C-6), 29.31 (t, C-7), 171.40 (s, C-1'), 33.01 (t, C-2'), 36.24 (t, C-3'), 36.80 (t, C-4');

$M^{+\cdot}$ 180, ($M^{+\cdot}$ - C_3H_6) 138, ($M^{+\cdot}$ - CO_2) 136.

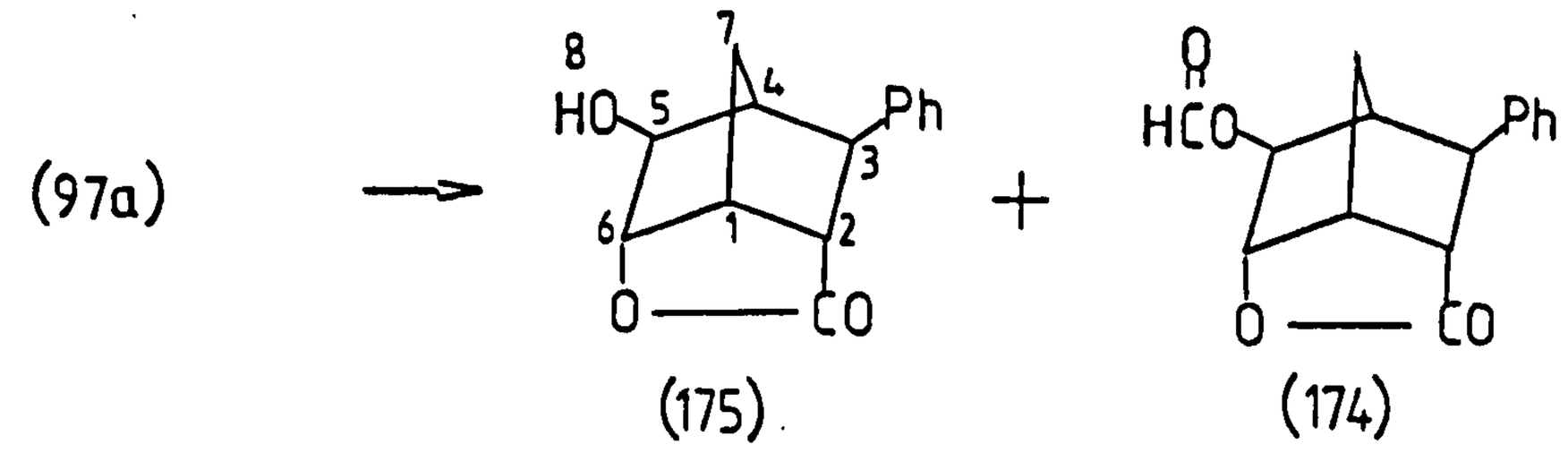
4.2.2.47. 3-exo-Phenylnorborn-5-en-2-endo-ylcarboxylic acid (97a).-



The endo-acid (97a) was prepared, by reaction of the γ-lactone (128) (6.0 g, 0.018 mole) in acetic acid (18 ml) with zinc powder (8.0 g) by the method of Berson and Ben-Efraim;[129] yield (2.80 g, 0.013 mole, 74.10%) as a white crystalline solid (methanol/water) m.p. 105-106°. (Lit.[119] m.p. 107-108°).

νmax cm^{-1} (Nujol) 3300 (br, COOH), 1710 (s, C = O); δ(60 MHz, $CDCl_3$) 7.30 (m, C_6H_5), 6.30 (m, H-5, H-6), 3.35 (m, H-1, H-4, H-2exo), 3.0 (brs, H-3endo), 1.70 (m, H-7syn, H-7anti).

4.2.2.48. Reaction of 3-exo-Phenylnorborn-5-en-2-endo-ylcarboxylic acid (97a) with Hydrogen Peroxide in Formic Acid.-



Hydrogen peroxide (1.02 g, 100 vol) was added dropwise over 5 min under a nitrogen atmosphere, and with stirring, to a solution of the acid (57) (1.30 g, 6.0 mmole) in formic acid (Analar 98-100%) (3.0 g, 60 mmole) at 45°. The resultant homogenous solution was heated at 45-50° for 1 h, cooled, and chloroform (30 ml) added. The solution was washed with 0.5 N sodium hydrogen carbornate (5 x 20 ml), water (2 x 20 ml), dried ($MgSO_4$) and the solvent evaporated to afford a yellow oil (0.80 g). Separation by p.l.c. (chloroform, 60 x 20 x 0.1 cm silica gel plates), afforded the following compounds:

(i) 6-endo, 5-exo-Dihydroxy-3-exo-phenylnorborn-2-endo-ylcarboxylic acid γ-lactone (175) (0.56 g, 2.43 mmole), R_F = 0.45, as a white crystalline solid m.p. 80-82° on recrystallisation from carbon tetrachloride.

νmax cm^{-1} ($CHCl_3$) 3480 (m, OH), 1780 (s, C = O), 1600 (m, Aromatic);

δ(60 MHz, $CDCl_3$) 7.25 (m, C_6H_5), 4.45 (brd, H-6exo), 3.85 (brs, H-5endo) 3.70 (brs, H-8), 3.10 (m, H-1, H-4), 2.80 (m, H-2exo, H-3endo), 1.92 (m, H-7syn, H-7anti);

J(Hz) (6-exo, 1) 5;

$M^{+\cdot}$ 230, ($M^{+\cdot}$ - H_2O) 212, ($M^{+\cdot}$ - CO) 202.

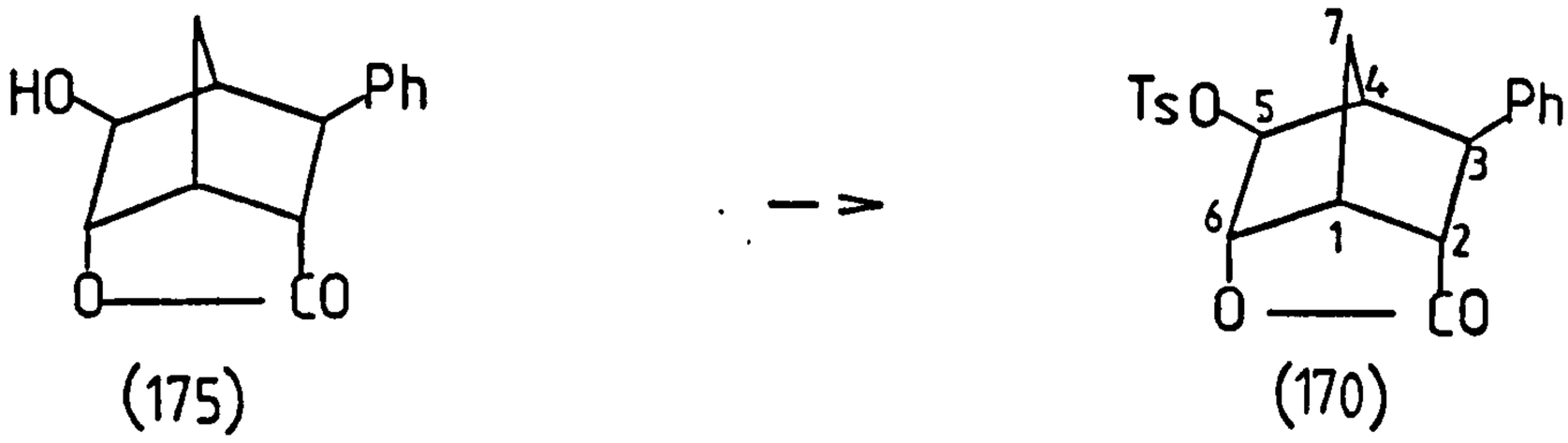
(ii) 6-endo-Hydroxy-3-exo-phenyl-5-exo-formyloxynorborn-2-endo-ylcarboxylic acid γ-lactone (174) (0.15 g, 0.58 mmole), R_F = 0.75, as a white solid, m.p. 70-73°.

νmax cm^{-1} ($CHCl_3$) 1785 (s, C = O), 1730 (s, C = O), 1600 (m, Aromatic);

δ(60MHz, $CDCl_3$) 8.05 (s, H-8), 7.25 (m, C_6H_5), 4.83

(brs, H-5 endo), 4.60 (d, H-6exo), 3.20 (m, H-1, H-4), 2.80 (m, H-2exo, H-3endo), 1.95 (m, H-7anti, H-7syn); J(Hz), (6-exo, 1) 5;
$M^{+\cdot}$ 258, ($M^{+\cdot}$ - CO) 230, ($M^{+\cdot}$ - HCOOH) 212.

4.2.2.49. 6-endo-Hydroxy-3-exo-phenyl-5-exo-tosyloxy-norborn-2-endo-ylcarboxylic acid γ-lactone (170).—



A solution of the hydroxy lactone (175) (0.26 g, 1.1 mmole) in pyridine (5 ml) was cooled and stirred in an ice-salt bath. Tosyl chloride (0.90 g, 47 mmole) was added slowly and the resultant yellow solution kept in a refrigerator for 40 h. The product was worked up as in reaction 4.2.2.10 Method (iii), Step 2, to give 6-endo-hydroxy-3-exo-phenyl-5-exo-tosyloxynorborn-2-endo-ylcarboxylic acid γ-lactone (170), (0.28 g, 0.74 mmole, 73.9%), as a white crystalline solid, m.p. 161-163° on recrystallisation from ethyl acetate/light petroleum b.p. 60-80°.

νmax cm^{-1} ($CHCl_3$) 1800 (s, C = O), 1600 (m, Aromatic);
δ(90 MHz, $CDCl_3$) 7.83 (d, Aromatic), 7.35 (d, Aromatic), 7.19 (m, C_6H_5), 4.56 (d, H-6exo), 4.40 (brs, H-5endo), 3.15(m, H-1, H-4), 2.84 (brs, H-2exo, H-3endo), 2.47 (s, CH_3), 1.99 (brs, H-7anti, H-7syn);

J(Hz) (1,6-exo) 3, (ortho-Aromatic-H, meta-Aromatic - H) 8, $M^{+\cdot}$ 384, ($M^{+\cdot}$ - $C_7H_7SO_2$) 229, ($M^{+\cdot}$ - $C_7H_7SO_2OH$) 212.

4.2.2.50. General method for reaction of iodolactones with silver tosylate.-

A solution of iodolactone (10 mmole) in anhydrous acetonitrile (20 ml) was added dropwise over 1 h to a well stirred solution of silver tosylate[50] (30 mmole) in anhydrous acetonitrile (40 ml) cooled in an ice-bath to 5° and protected from light under a nitrogen atmosphere. After the addition was completed the stirred solution was kept at 5° for a further 1 h and then allowed to reach room temperature over the next hour. The reaction mixture was then heated at a particular temperature for a stated time as a yellow precipitate of silver iodide gradually formed. The acetonitrile solution was decanted, the silver iodide precipitate washed with water (40 ml), and the washings added to the acetonitrile solution. The resultant solution was extracted with dichloromethane (4 x 60 ml), the extracts combined and filtered through celite. The filtrate was washed with water (2 x 60 ml), dried ($MgSO_4$), filtered and the solvent evaporated to afford the product.

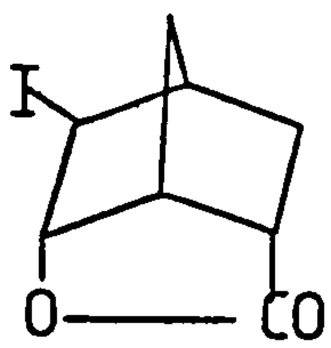
4.2.2.51. Preparation of silver tosylate.-

$$AgNO_3 + NaOTs \longrightarrow AgOTs + NaNO_3$$

Silver tosylate was prepared from sodium toluene-p-sulphonate (58.20 g, 0.30 mole) in water (200 ml) and

silver nitrate (50.96 g, 0.3 mole) in water (200 ml) by the method of Hoffmann;[50] yield (48.2 g, 0.17 mole, 57.6%) as a white-grey shining solid.

4.2.2.52. Reaction of 6-endo-Hydroxy-5-exo-iodonorborn-2-endo-ylcarboxylic acid γ-lactone (122) with silver tosylate.-



(122)

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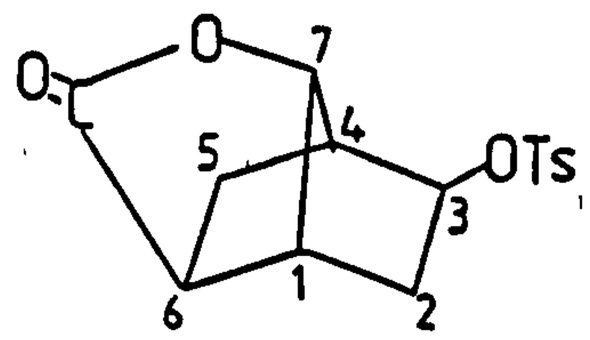


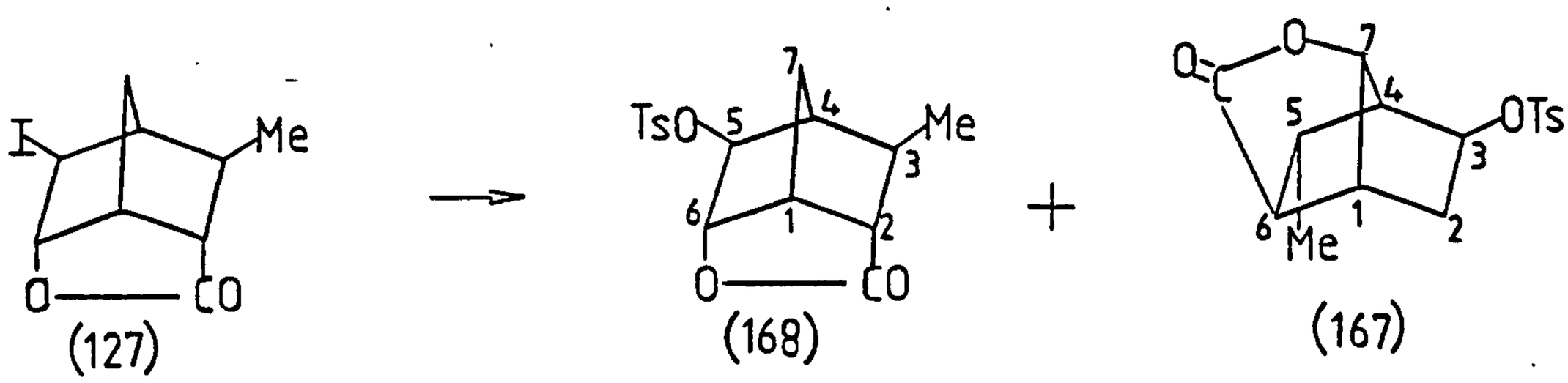
(166)

A solution of the γ-iodolactone (122) (2.0 g, 7.6 mmole) in anhydrous acetonitrile (11 ml) was added to a solution of silver tosylate (4.0 g, 14.3 mmole) in anhydrous acetonitrile (18 ml) as in 4.2.2.50. The reaction mixture was then heated at reflux for 8 h and worked up as in 4.2.2.50 to give a yellow oil (2.0 g). Separation by p.l.c. (chloroform, 60 x 20 x 0.1 cm silica gel plates), gave the unreacted γ-iodolactone (122) (0.5 g, 1.9 mmole), as a white solid m.p. 57-59° and 7-syn-hydroxy-3-exo-tosyloxynorborn-6-exo-ylcarboxylic acid γ-lactone (166) as a clear oil (1.30 g, 4.2 mmole) which crystallised on standing to afford, after recrystallisation from light petroleum b.p. 60-80°, white crystals m.p. 103-105°.

Found: C, 58.13; H, 5.32. $C_{15}H_{16}O_5S$ requires C, 58.44; H, 5.19%.

νmax cm^{-1} ($CHCl_3$) 1790 (s, C = O), 1600 (m, Aromatic); δ(90 MHz, $CDCl_3$) 7.79 (d, Aromatic-H), 7.36 (d, Aromatic-H), 4.99 (brs, H-7anti), 4.69 (brd, H-3endo), 2.66 (m, H-6endo, H-1, H-4), 2.46 (s, CH_3), 1.8 (m, H-2endo, H-2exo, H-5exo), 1.33 (brq, H-5endo);
J(Hz) (ortho-Aromatic-H, meta-Aromatic-H) 8, (2-endo, 3-endo) 6, (5-endo, 6-endo) 6, (5-endo, 6-exo) 14;
$M^{+\cdot}$ 308.

4.2.2.53. Reaction of 6-endo-Hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylcarboxylic acid γ-lactone (127) with silver tosylate.-



A solution of the γ-iodolactone (127) (1.02 g, 4 mmole) in anhydrous acetonitrile (12 ml) was added to a solution of silver tosylate (4.0 g, 14.3 mmole) in anhydrous acetonitrile (30 ml) as in 4.2.2.50. The reaction mixture was then heated at reflux for 40 h and worked up as in 4.2.2.50 to give a semi-solid product (0.70 g). Separation by p.l.c. (2:3 ethyl acetate/ light petroleum b.p. 60-80°, 60 x 20 x 0.1 cm silica gel plates), gave the following compounds:

(i) The unreacted γ-iodolactone (127) (0.18 g, 0.71 mmole), R_F = 0.75, as white crystals, m.p. 52-54°.

(ii) 6-endo-Hydroxy-3-exo-methyl-5-exo-tosyloxynorborn-2-endo-ylcarboxylic acid γ-lactone (168) (0.27 g, 0.83 mmole)

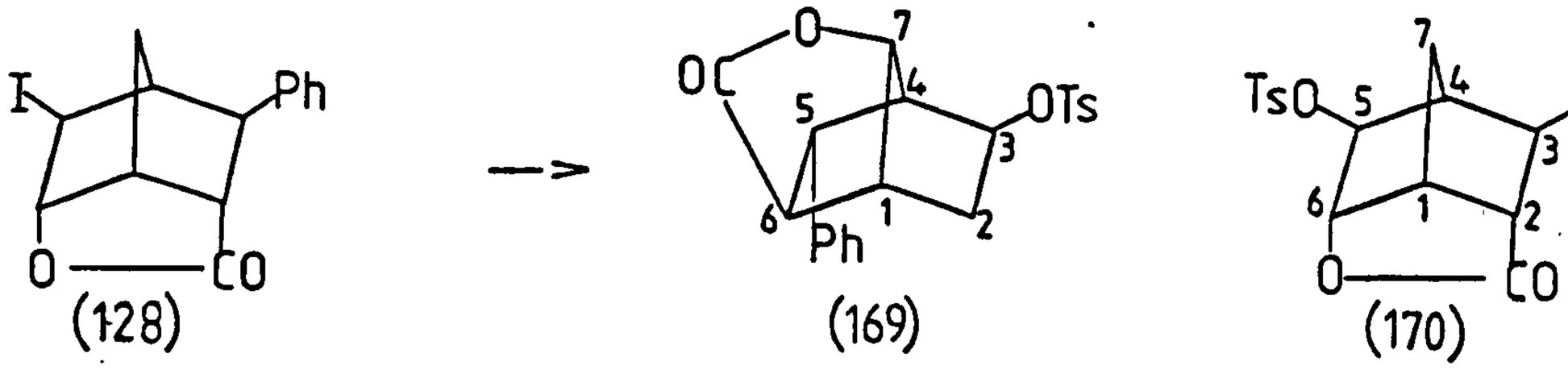
R_F = 0.52 as a white crystalline solid m.p. 77-78° on recrystallisation from pentane-ether. Found: C, 59.63; H, 5.67, S, 9.83. $C_{16}H_{18}O_5S$ requires C, 59.63; H, 5.59, S, 9.94%.

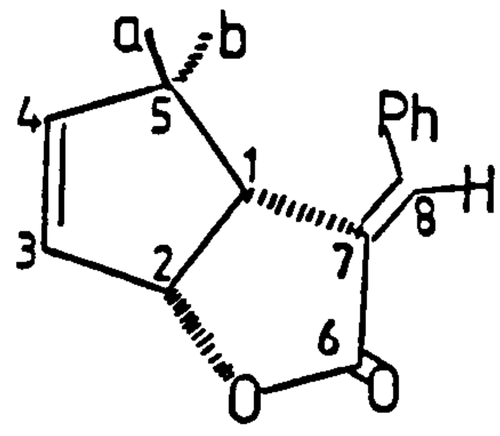
νmax cm^{-1} ($CHCl_3$) 1790 (s, C = O), 1600 (m, Aromatic); δ(90 MHz, $CDCl_3$) 7.75 (d, Aromatic-H), 7.35 (d, Aromatic-H), 4.45 (brd, H-6exo), 4.22 (brs, H-5endo), 3.13 (brt, H-1), 2.46 (s, CH_3), 2.13 (brs, H-4), 2.06 (brd, H-2exo), 1.89 (m, H-7anti, H-7syn), 1.78 (m, H-3endo), 1.09 (d, CH_3); J(Hz) (6-exo, 1) 6, (2-exo, 1) 6, (ortho-Aromatic-H, meta-Aromatic-H) 8, (CH_3, 3-endo) 8;
$M^{+\cdot}$ 322, ($M^{+\cdot}$ - CH_3) 307, ($M^{+\cdot}$ - $C_7H_7SO_2$) 151.

(iii) 7-syn-Hydroxy-5-endo-methyl-3-exo-tosyloxynorborn-6-exo-ylcarboxylic acid γ-lactone (167) (0.11 g, 0.34 mmole) R_F = 0.43, as a white crystalline solid m.p. 115-117° on recrystallisation from pentane-ether.
Found: C, 59.66; H, 5.75, S, 9.65. $C_{16}H_{18}O_5S$ requires C, 59.63; H, 5.59, S, 9.94%.

νmax cm^{-1} ($CHCl_3$) 1780 (s, C = O), 1600 (m, Aromatic); δ(90 MHz, $CDCl_3$) 7.75 (d, Aromatic-H), 7.35 (d, Aromatic-H), 5.03 (brs, H-7anti), 4.85 (brq, H-3endo), 2.69 (m, H-6endo), 2.54 (brd, H-1), 2.46 (s, CH_3), 2.28 (m, H-4), 2.23 (m, H-2exo), 2.03 (q, H-2endo), 1.90 (brd, H-5exo), 1.07 (d, CH_3);
J(Hz) (3-endo, 2-endo) 6, (1,2-exo) 6, (5-exo, 4) 5, (CH_3, 5-exo) 7;
$M^{+\cdot}$ 322, ($M^{+\cdot}$ - CH_3) 307, ($M^{+\cdot}$ - CO) 314.

4.2.2.54. Reaction of 6-endo-Hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo-ylcarboxylic acid γ-lactone (128) with silver tosylate.—





A solution of the γ-iodolactone (128) (1.0 g, 2.9 mmole) in anhydrous acetonitrile (20 ml) was added to a solution of silver tosylate (3.23 g, 11.6 mmole) in anhydrous acetonitrile (30 ml) as in 4.2.2.50. The reaction mixture was then heated at reflux for 48 h and worked up as in 4.2.2.50 to afford a yellowish brown oily residue (0.543 g). Separation by p.l.c. (3:7 ethyl acetate/light petroleum b.p. 60-80°, 60 x 20 x 0.1 cm silica gel plate) gave the following compounds:

(i) α-(cis-2-hydroxycyclopent-3-en-1-yl)-E-cinnamic acid γ-lactone (171) (0.30 g, 1.41 mmole), R_F 0.43, as a white crystalline solid m.p. 107-108° on recrystallisation from 1:9 ethyl acetate/light petroleum b.p. 60-80°. Found: C, 79.03; H, 5.59. $C_{14}H_{14}O_2$ requires C, 79.24; H, 5.66%;

νmax cm^{-1} ($CHCl_3$) 1760 (s, C = O), 1650 (m, C = C); δ(90 MHz, $CDCl_3$) 7.50 (m, Ph, H-8), 6.06 (m, H-3), 5.94 (m, H-4), 5.60 (dxm, H-2), 4.07 (m, H-1), 3.11 (qxm, H-5a), 2.43 (dxm, H-5b); J(Hz) (5a, 5b) 19, (1,5a) 9.5, (1, 5b) 4, (2, 3) 2, (2, 4) 2, (3, 4) 6, (3, 5a) 2, (3, 5b) 1, (4, 5a) 2, (4, 5b) 2; uv λmax (CH_3OH) 284 nm (ε = 21,284); $M^{+\cdot}$ 212.

(ii) 6-endo-Hydroxy-3-exo-phenyl-5-exo-tosyloxynorborn-2-endo-ylcarboxylic acid γ-lactone (170) (0.15 g, 0.39 mmole) R_F 0.35, as a white crystalline solid m.p. 161-163° on recrystallisation from 1:9 ethyl acetate/light petroleum b.p. 60-80°.

Found: C, 65.76; H, 5.28. $C_{21}H_{21}O_5S$ requires C, 65.45. H, 5.45%.

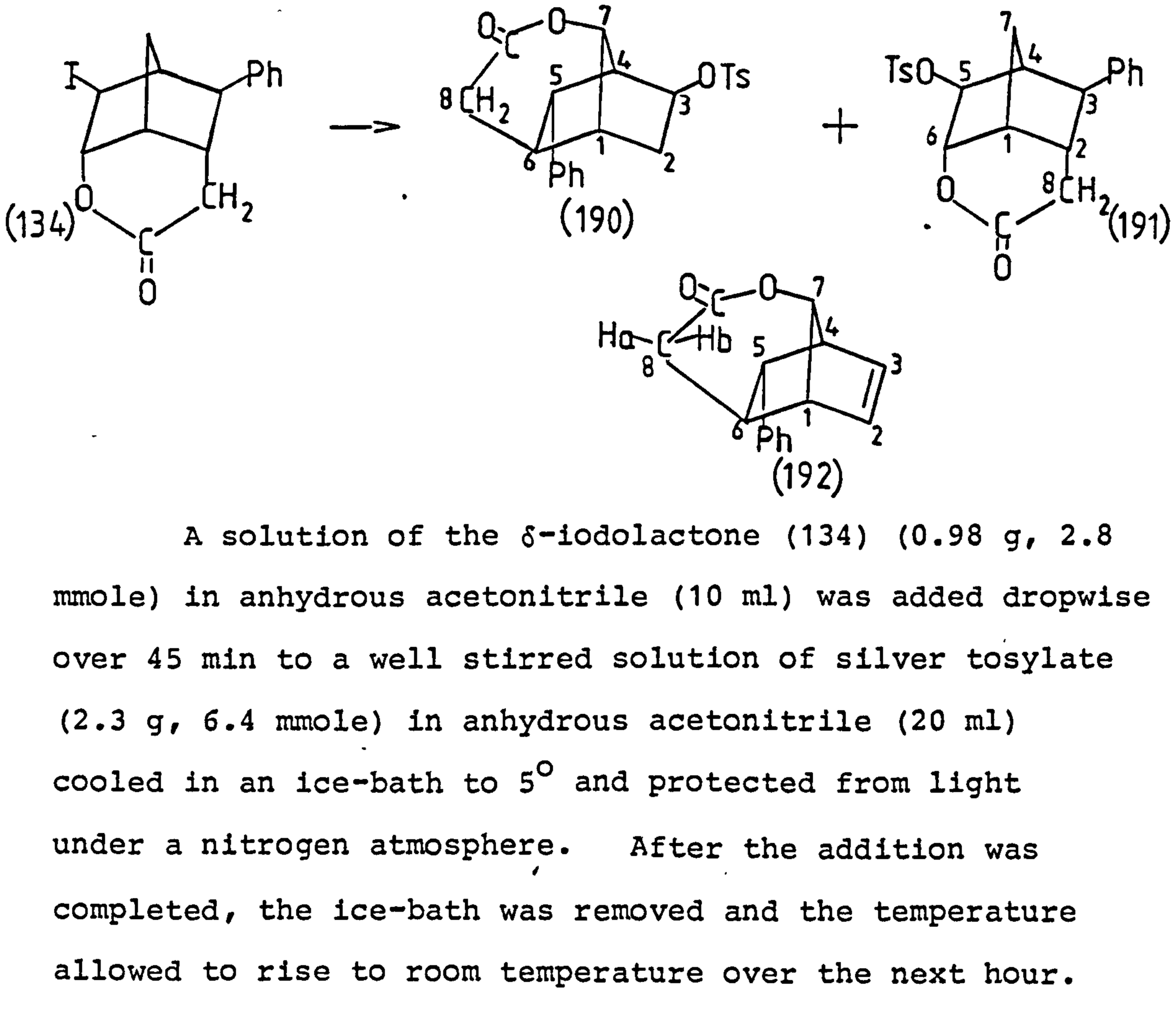
νmax cm^{-1} ($CHCl_3$) 1800 (s, C = O), 1600 (m, Aromatic); δ(90 MHz, $CDCl_3$) 7.83 (d, Aromatic-H), 7.35 (d, Aromatic-H), 7.19 (m, Ph), 4.56 (d, H-6exo), 4.40 (brs, H-5endo), 3.15 (m, H-1 and H-4), 2.84 (brs, H-2exo, H-3endo), 2.47 (s, CH_3), 1.99 (brs, H-7syn, H-7anti); J(Hz) (1, 6-exo) 3, (ortho-Aromatic-H, meta-Aromatic-H) 8; $M^{+\cdot}$ 384, ($M^{+\cdot}$ - $C_7H_7SO_2$) 229, ($M^{+\cdot}$ - $C_7H_7SO_2OH$) 212.

(iii) 7-syn-Hydroxy-5-endo-phenyl-3-exo-tosyloxynorborn-6-exo-ylcarboxylic acid γ-lactone (169) (70.8 mg, 0.18 mmole) R_F = 0.25, as a white crystalline solid m.p. 130.5-132° on recrystallisation from ethyl acetate.

Found: C, 65.80; H, 5.19. $C_{21}H_{21}O_5S$ requires C, 65.45; H, 5.45%.

νmax cm^{-1} ($CHCl_3$) 1790 (s, C = O), 1598 (m, Aromatic);
δ(90 MHz, $CDCl_3$) 7.62 (d, Aromatic-H), 7.30 (m, C_6H_5),
7.12 (d, Aromatic-H), 5.15 (brs, H-7anti0, 4.08 (d, H-3endo),
3.41 (d, H-5exo), 3.18 (t, H-6endo), 2.90 (m, H-4, H-1),
2.42 (s, CH_3), 1.96 (q, H-2endo), 1.65 (m, H-2exo);
J(Hz) (2-endo, 3-endo) 6, (2-endo, 2-exo) 16, (H, 5-exo) 6,
(5-exo, 6-endo) 2, (6-endo, 7-anti) 2, (ortho-Aromatic-H,
meta-Aromatic-H) 9;
$M^{+\cdot}$ 384, ($M^{+\cdot}$ - $C_7H_7SO_2$) 229, ($M^{+\cdot}$ - $C_7H_7SO_2OH$) 212.

4.2.2.55. Reaction of 6-endo-Hydroxy-5-exo-iodo-3-exo-phenylnorborn-2-endo-ylcarboxylic acid δ-lactone (134) with silver tosylate.—



A solution of the δ-iodolactone (134) (0.98 g, 2.8 mmole) in anhydrous acetonitrile (10 ml) was added dropwise over 45 min to a well stirred solution of silver tosylate (2.3 g, 6.4 mmole) in anhydrous acetonitrile (20 ml) cooled in an ice-bath to 5° and protected from light under a nitrogen atmosphere. After the addition was completed, the ice-bath was removed and the temperature allowed to rise to room temperature over the next hour.

The reaction mixture was then heated at 55° for 16 h and worked up as 4.2.2.50 to afford a yellow oil (0.94 g). Separation by column chromatography [50 g of Silica gel Merck H Type 60] with 2:3 ethyl acetate/light petroleum b.p. 60-80° as eluent gave the following compounds:

(i) 6-endo-Hydroxy-3-exo-phenyl-5-exo-tosyloxynorborn-2-endo-ylacetic acid δ-lactone (191) (0.40 g, 1 mmole) R_F = 0.39 as a white crystalline solid, m.p. 188-189°. Found: C, 66.05; H, 5.63; S, 7.83. $C_{22}H_{22}O_5S$ requires C, 66.33; H, 5.53; S, 8.04%.

νmax cm^{-1} ($CHCl_3$) 1734 (s, C = O), 1598 (m, Aromatic); δ(90 MHz, $CDCl_3$) 7.80 (d, Aromatic-H), 7.32 (d, Aromatic-H), 7.22 (m, C_6H_5), 4.69 (d, H-6exo), 4.42 (brs, H-5endo), 2.66 (brd, H-3endo, H-8a, H-8b), 2.57 (m, H-4), 2.44 (s, CH_3), 2.36 (m, H-1), 2.32 (m, H-2exo), 1.97 (m, H-7anti, H-7syn);
J(Hz) (6-exo, 1) 4, (ortho-Aromatic-H, meta-Aromatic-H) 8;
$M^{+\cdot}$ 398, ($M^{+\cdot}$ - $C_7H_7OSO_2$) 226, ($M^{+\cdot}$ - $C_7H_7SO_2$ - C_6H_5) 165.

(ii) 7-syn-Hydroxy-5-endo-phenyl-3-exo-tosyloxynorborn-6-exo-ylacetic acid δ-lactone (190) (0.32 g, 0.8 mmole) R_F = 0.26 as white crystals, m.p. 191-192°. Found: C, 66.25; H, 5.68; S, 7.84. $C_{22}H_{22}O_5S$ requires C, 66.33; H, 5.53; S, 7.84%.

νmax cm^{-1} ($CHCl_3$) 1738 (s, C = O);
δ(90 MHz, $CDCl_3$) 7.46 (d, Aromatic-H), 7.30 (d, Aromatic-H), 7.11 (m, C_6H_5), 4.92 (brd, H-7anti), 4.02 (t, H-3endo), 3.15 (d, H-5exo), 2.77 (d, H-4), 2.66 (brd, H-8a, H-8b), 2.49 (d, H-6-endo), 2.43 (s, CH_3), 2.29 (brs, H -1),

1.89 (m, H-2exo; H-2endo);

J(Hz) (ortho-Aromatic-H, meta-Aromatic-H) 8, (3-endo, 2-endo) 5, (3-endo, 2-exo) 5, (7-syn, 6-endo) 2, (5-exo, 4) 5;

$M^{+\cdot}$ 398, ($M^{+\cdot}$ - $C_7H_7SO_2OH$) 217.

(iii) 7-anti-Hydroxy-5-endo-phenylnorborn-2-en-6-exo-ylacetic acid δ-lactone (192) (60 mg, 0.265 mmole)

R_F = 0.58 as a colourless oil, b.p. 150° at 0.08 Hg.

Found: C, 79.44; H, 6.14. $C_{15}H_{14}O_2$ requires C, 79.05; H, 6.19%.

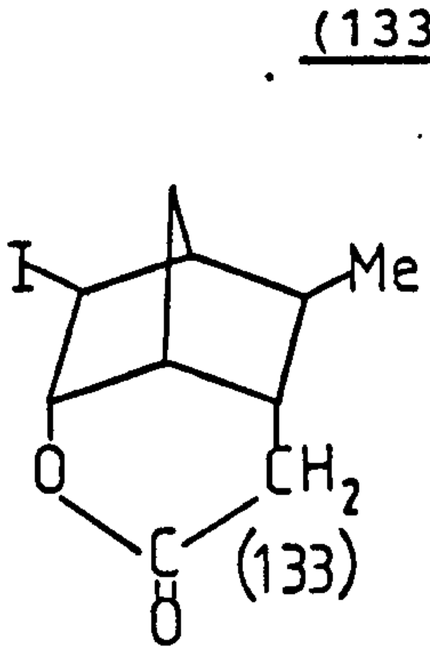
νmax cm^{-1} ($CHCl_3$) 1735 (s, C = O);

δ(90 MHz, $CDCl_3$) 7.20 (m, C_6H_5), 6.24 (q, H-2), 5.77 (q, H-3) 4.33 (d, H-7syn), 3.25 (m, H-5exo, H-4), 3.0 (q, H-8b), 2.78 (brs, H-1), 2.71 (q, H-8a), 2.39 (m, H-6-endo);

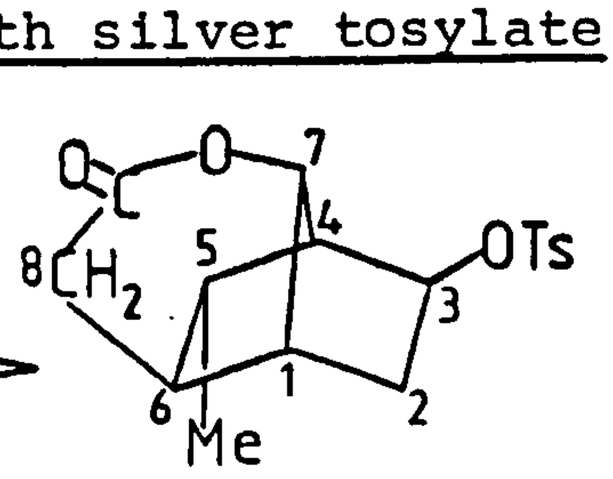
J(Hz) (2,3) 6, (7-syn, 6-endo) 3, (6-endo, 5-exo) 4, (8a, 8b) 17, (8a, 6-endo) 4, (8b, 6-endo) 4;

$M^{+\cdot}$ 226, ($M^{+\cdot}$ - CH_3CO_2H) 166, ($C_{10}H_8O_2^{+\cdot}$) 160

4.2.2.56. Reaction of 6-endo-Hydroxy-5-exo-iodo-3-exo-methylnorborn-2-endo-ylcarboxylic acid δ-lactone (133) with silver tosylate.–

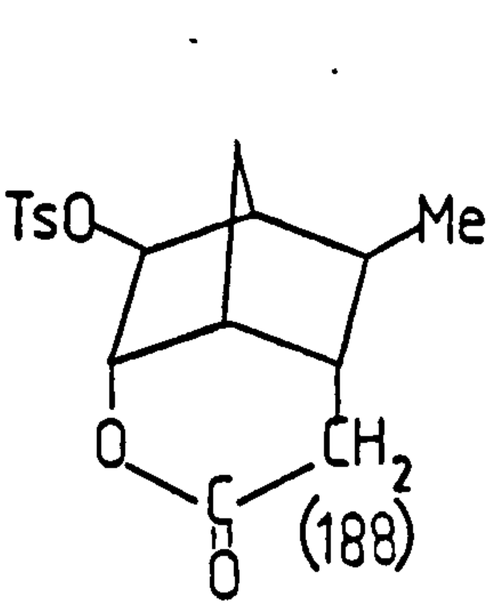


(133)

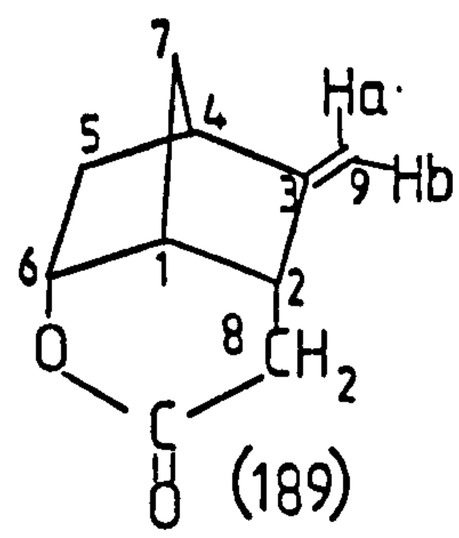


(187)

+



(188)



(189)

A solution of the δ-iodolactone (133) (2.4 g, 82 mmole) in anhydrous acetonitrile (20 ml) was added dropwise over 45 min to a well stirred solution of silver tolsylate (6.3 g, 23 mmole) in anhydrous acetonitrile (35 ml) cooled in an ice-bath to 5° and protected from light under a nitrogen atmosphere. After the addition was complete, the ice bath was removed and the temperature allowed to rise to room temperature over the next hour. The reaction mixture was then stirred at room temperature for 16 h and worked up as 4.2.2.50 to afford a yellow oil (1.5 g). Separation by p.l.c. [2:3 ethyl acetate/ light petroleum b.p. 60-80°, 60 x 20 x 0.1 cm silica gel plates], gave the following compounds:

(i) 6-endo-Hydroxy-3-methylenenorborn-2-endo-ylacetic acid δ-lactone (189) (0.48 g, 2.93 mmole) R_F = 0.47, as a pale yellow oil. Found: C, 72.95; H, 7.31. $C_{10}H_{12}O_2$ requires C, 73.17; H, 7.31%.

νmax cm^{-1} ($CHCl_3$) 1735 (s, C = O);

δ(90 MHz, $CDCl_3$) 5.05 (d, H-9a), 4.94 (m, H-6exo), 4.82 (d, H-9b), 2.75 (m, H-8a, H-8b, H-4, H-1), 2.54 (m, H-2exo), 2.22 (dxq, H-5exo), 1.57 (m, H-7anti, H-7syn), 1.40 (dxt, H-5endo);

J(Hz) (9a, 9b) 2, (5-exo, 5-endo) 14, (5-exo, 6-exo) 10, (5-exo,4) 4, (5-endo, H-7anti) 3;

$M^{+\cdot}$ 164, ($M^{+\cdot}$ - CO) 136, ($M^{+\cdot}$ - C_2H_2O) 122, ($M^{+\cdot}$ - $C_3H_3O_2$) 92.

(ii) 6-endo-Hydroxy-3-exo-methyl-5-exo-tosyloxynorborn-2-endo-ylacetic acid δ-lactone (188) (0.42 g, 1.25 mmole) R_F = 0.27, as a white crystalline solid, m.p. 132-134° on recrystallisation from ethyl acetate/light petroleum b.p. 60-80°. Found: C, 60.65; H, 5.99; S, 9.32. $C_{17}H_{20}O_5S$ requires C, 60.71; H, 5.95; S, 9.32%.

νmax cm^{-1} ($CHCl_3$) 1735 (s, C = O);

δ(90 MHz, $CDCl_3$) 7.75 (d, Aromatic-H), 7.35 (d, Aromatic-H), 4.80 (q, H-6exo), 4.72 (d, H-5endo), 2.57 (d, H-8a, H-8b), 2.46 (s, CH_3), 2.42 (brs, H-4), 2.13 (m, H-1), 1.90 (m, H-7anti, H-7syn), 1.82 (d, H-3endo), 1.53 (m, H-2exo), 1.0 (d, CH_3);

J(Hz) (CH_3, H-3endo) 8, (ortho-Aromatic-H, meta-Aromatic-H) 8, (8,2-exo) 3, (6-exo, 1) 6, (5-endo, H-7anti) 3.

$M^{+\cdot}$ 336, ($M^{+\cdot}$ - CH_3) 321, ($M^{+\cdot}$ - $C_7H_7SO_3$) 164.

(iii) 7-syn-Hydroxy-5-endo-methyl-3-exo-tosyloxynorborn-6-exo-ylacetic acid δ-lactone (187) (0.3 g, 0.89 mmole) R_F = 0.33 as a white crystalline solid m.p. 140-141° on recrystallisation from ethyl acetate/light petroleum b.p. 60-80°. Found: C, 60.38; H, 5.75; S, 9.18. $C_{17}H_{20}O_5S$ requires C, 60.71; H, 5.95; S, 9.32.

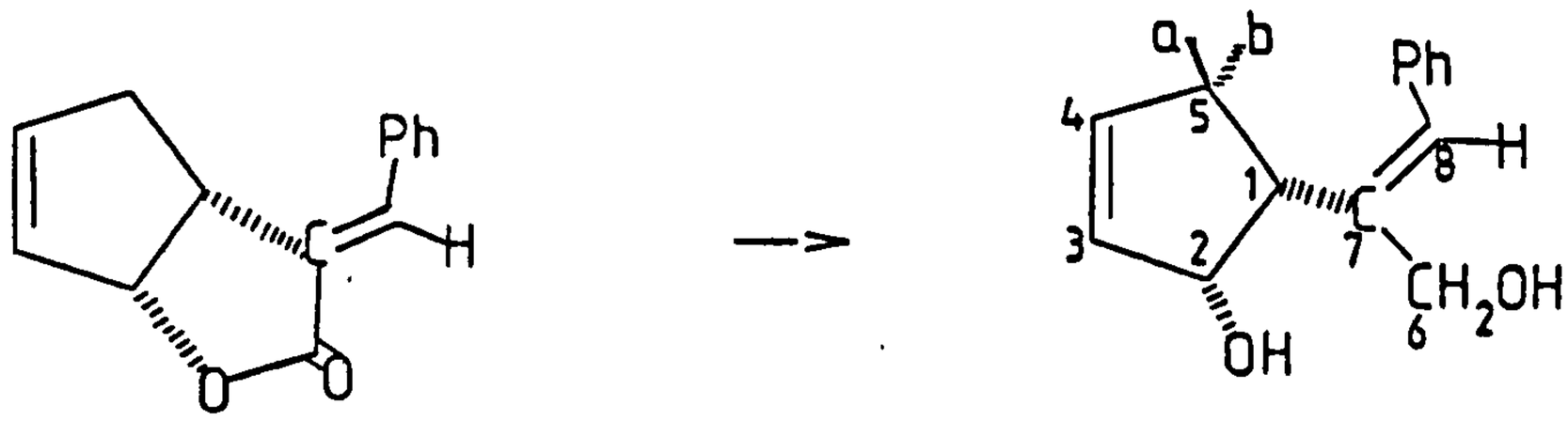
νmax cm^{-1} ($CHCl_3$) 1735 (s, C = O);

δ(90 MHz, $CDCl_3$) 7.80 (d, Aromatic-H), 7.33 (d, Aromatic-H), 4.58 (d, H-3endo), 4.27 (brs, H-7anti), 2.54 (d, H-8a, H-8b), 2.44 (s, CH_3), 2.42 (brs, H-4), 2.10 (m, H-1), 1.70 (m, H-6-endo, H-2-exo, H-5exo), 1.0 (d, CH_3);

J(Hz) (ortho-Aromatic-H, meta-Aromatic-H) 8, (8, 6-endo) 3, (CH_3, 5-exo) 6.

$M^{+\cdot}$ 366, ($M^{+\cdot}$ - CH_3) 351.

4.2.2.57. α-(cis-2-hydroxycyclopent-3-en-1-yl)-E-cinnamoyl alcohol (172).-

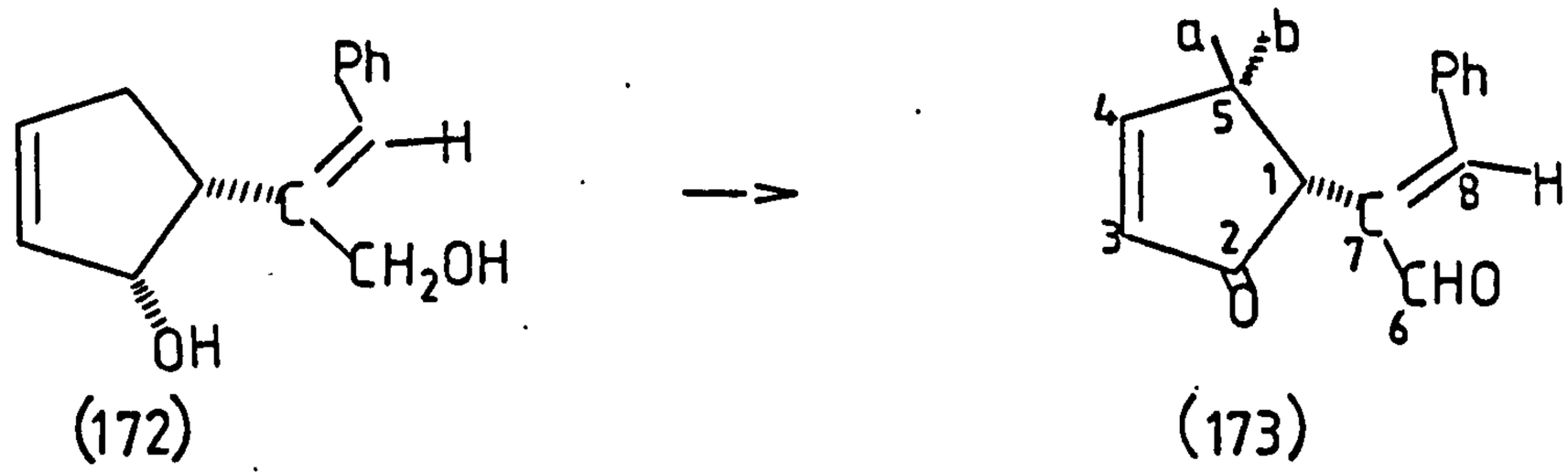


(171) (172)

A solution of the γ-lactone (171) (0.14 g, 0.66 mole) in anhydrous ether (10 ml) was added dropwise over 0.5 h to a stirred suspension of lithium aluminum hydride (0.1 g, 2.6 mmole) in anhydrous ether (40 ml). After stirring for a further 1.5 h a saturated solution of ammonium chloride (15 ml) was added dropwise until a granular precipitate of inorganic salts had formed. The mixture was filtered, the filtrate dried ($MgSO_4$) and the solvent evaporated to afford the diol (172) as a colourless viscous liquid solidifying on standing to afford crystals (0.114 g, 0.53 mole) m.p. 75-77° on recrystallisation from light petroleum b.p. 60-80°. Found: C, 77.43; H, 7.21. $C_{14}H_{16}O_2$ requires C, 77.78; H, 7.41%.

νmax cm^{-1} ($CHCl_3$) 3380 (m, OH), 1600 (m, Aromatic); δ(90 MHz, $CDCl_3$) 7.19 (m, C_6H_5), 6.60 (s, H-8), 5.70 (m, H-3, H-4), 4.60 (d, H-2), 4.40 (brs, OH), 4.10 (dxd, H-6), 3.46 (m, H-1), 2.41 (dxm, H-5a), 2.26 (m, H-5b); J(Hz) (5a, 5b) 17, (1,2) 7.5, (6a, 6b) 12.5; $M^{+\cdot}$ 216, ($M^{+\cdot}$ - OH) 199, ($M^{+\cdot}$ - CH_2OH) 183, ($M^{+\cdot}$ - OH-CH_2OH) 168.

4.2.2.58. α-(cis-2-one-cyclopent-3-en-1-yl)-E-cinnamaldehyde (173).-



(172) (173)

To a well stirred solution of pyridinium dichromate[140] (3.2 g, 8.5 mmole) in anhydrous dimethylformamide (12 ml) was added a solution of the diol (172) (0.263 g, 1.22 mmole) in anhydrous dimethylformamide, the reaction was carried out under a nitrogen atmosphere in a 3-neck flask (100 ml). After 5 h at room temperature, the reaction mixture was diluted with water (120 ml) and then extracted with chloroform (6 x 30 ml). The combined extracts were washed with water (2 x 30 ml), dried ($MgSO_4$) and the solvent evaporated to give a yellow oil which solidified on standing and was recrystallised from ethyl acetate-light petroleum b.p. 60-80° to afford keto-aldehyde (173) (0.19 g, 0.89 mmole, 73.6%) as white crystals, m.p. 133-135°. Found: C, 78.94; H, 5.62. $C_{14}H_{12}O_2$ requires C, 79.24; H, 5.66%.

νmax cm^{-1} ($CHCl_3$) 1710 (s, C = O), 1690 (s, CHO);

δ(90 MHz, $CDCl_3$) 9.50 (d, H-6), 7.74 (q, H-3), 7.65 (s, H-8), 7.43 (m, C_6H_5), 6.31 (dxt, H-4), 3.65 (t, H-1), 2.86 (m, H-5a, H-5b);

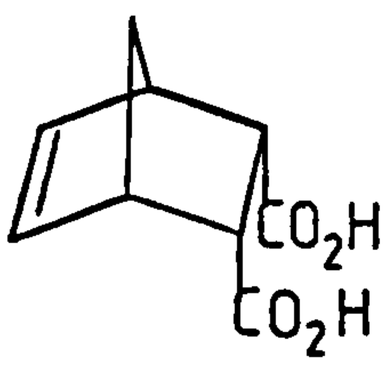
J(Hz) (1,5a) 5, (1,5b) 5, (3, 4) 6, (3,5a) 3, (4, 5a) 2.5,

(4-5b) 2.5, (1,6) 1;

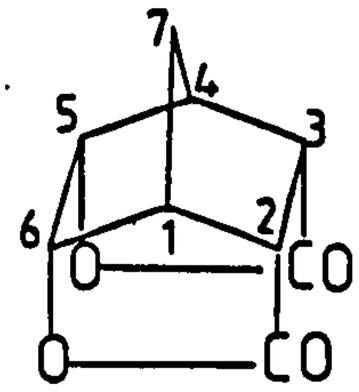
uv λmax (MeOH) 281 nm (ε = 15,759);

$M^{+\cdot}$ 212, ($M^{+\cdot}$ - CHO) 183, ($M^{+\cdot}$ - CHO - CO) 155.

4.3.1.1. 5-endo-6-endo-Dihydroxynorborn-2-endo,3-endo yldicarboxylic acid bis γ-lactone (255).—



(93)

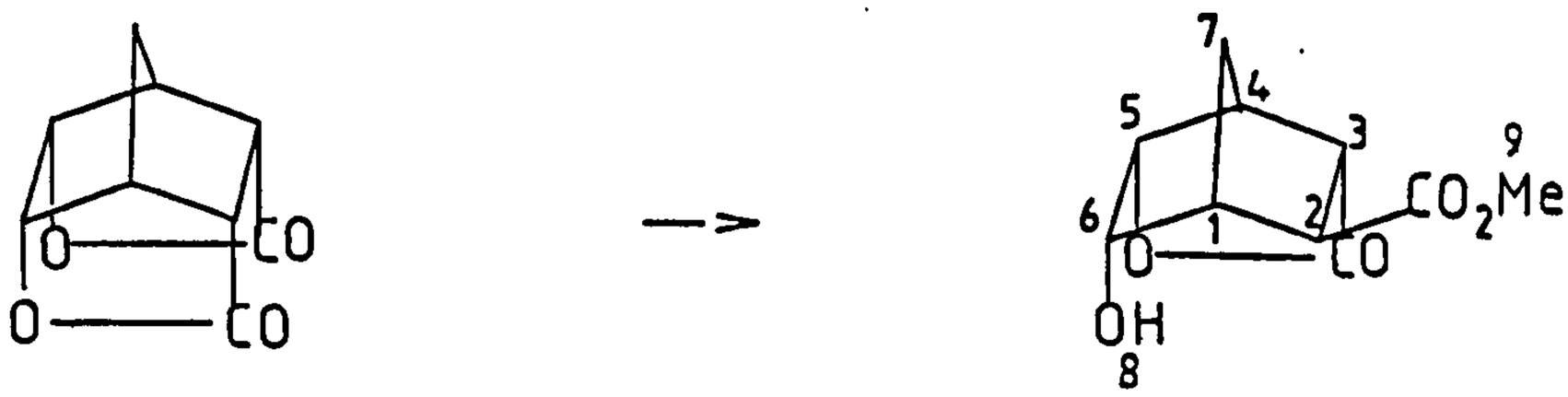


(255)

To a well stirred mixture of lead tetraacetate (86.0 g, 0.19 mole) in glacial acetic acid (90 ml) was added the cis-acid (93) (34.0 g, 0.187 mole). The mixture then was heated at 100°, and a clear solution was obtained after about 10 min. A few minutes later a white precipitate gradually formed and the mixture was heated for a further 2 h, cooled, the precipitate was filtered, washed with glacial acetic acid (10 ml), water (2 x 30 ml) and the product was recrystallised from water to afford the bis-γ-lactone (255) (22.4 g, 0.124 mole, 66.61%) as a white crystalline solid, m.p. 260-263°. (Lit. m.p. 264-265°)[178a] 274-275°[178b], 274-275.5,[178c] 265-266°,[178d] 264-266°,[178e] 263°[178f]).

νmax cm^{-1} ($CHCl_3$) 1800 (s, C = O), 1780 (s, C = O); δ(60 MHz, DMSO-d_6) 4.72 (m, H-5, H-6), 3.30 (m, H-1, H-4), 3.02 (m, H-2exo, H-3exo), 1.80 (m, H-7anti, H-7syn); $M^{+\cdot}$ 180, ($M^{+\cdot}$ - CO) 152, ($M^{+\cdot}$ - 2CO) 124.

4.3.1.2. 5-endo, 6-endo-Dihydroxy-2-exo-carbomethoxynorborn-3-endo-ylcarboxylic acid γ-lactone (256).-



(255) (256)

The bis-γ-lactone (255) (4.93 g, 0.03 mole) was added to a stirred solution of sodium methoxide [prepared from sodium (3.16 g, 0.14 mole) in anhydrous methanol] (108 ml) .

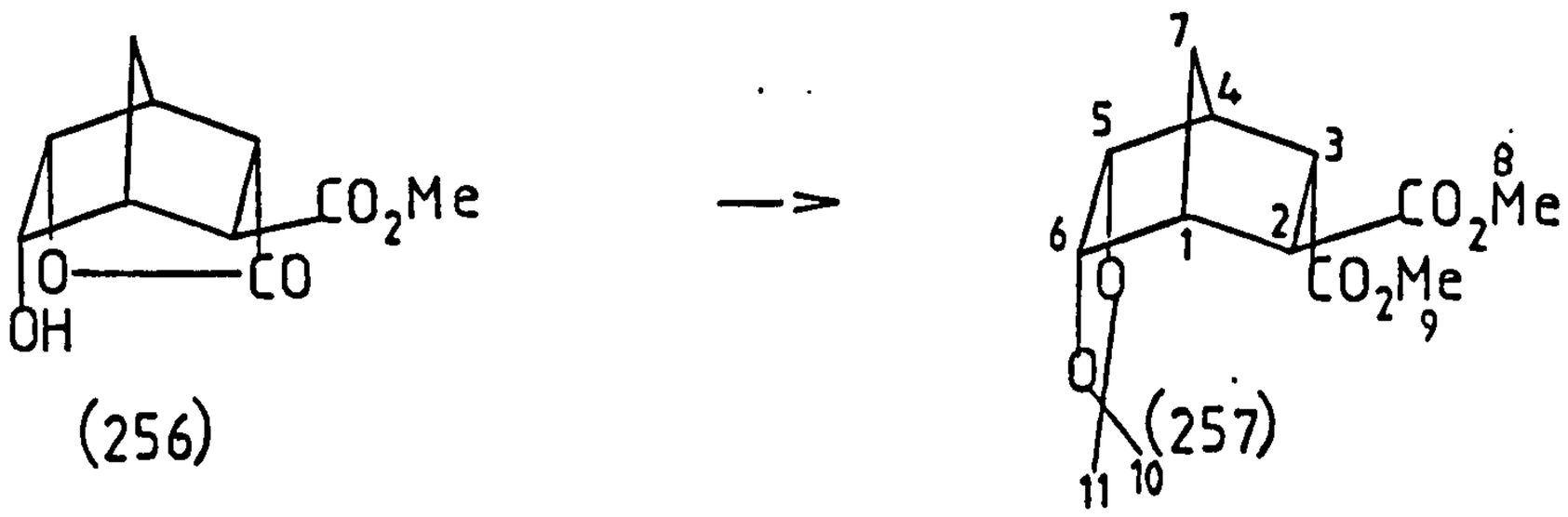
After 20 min a white precipitate gradually formed and the resultant mixture was stirred at room temperature under a nitrogen atmosphere for 24 h. The mixture was neutralised by the addition of Dowex 50W-X8 (H^+) ion exchange resin until the white precipitate dissolved. The ion exchange resin was filtered, washed with methanol (3 x 20 ml). The combined methanolic solution was evaporated to give pale yellow oil, which crystallised on standing. It was recrystallised from ethyl acetate/ light petroleum b.p. 60-80° to afford 5-endo, 6-endo-Dihydroxy-2-exo-carbomethoxynorborn-3-endo-ylcarboxylic acid γ-lactone (256) (4.78 g, 22.54 mmole, 82.5%) as a white crystalline solid, m.p. 75-77°. (Lit.[142] m.p. 75-76°).

νmax cm^{-1} ($CHCl_3$) 3530 (m, OH), 1770 (s, C = O), 1740 (s, C = O of ester);

δ(90 MHz, $CDCl_3$) 4.50 (t, H-5), 4.0 (q, H-6exo) , 3.65 (s, H-9), 3.47 (s, H-8), 3.15 (m, H-4), 3:04

(m, H-2endo) 3.01 (m, H-3exo), 2.72 (m, H-1), 1.62 (dxt, H-7anti), 1.40 (brd, H-7syn);
J(Hz) (5-exo, 6-exo) 6, (5-exo, 4) 6, (6-exo, 1) 4, (7-anti, 1) 2, (7-anti, 4) 2, (7-anti, 7-syn) 12;
$M^{+\cdot}$ 192, ($M^{+\cdot}$ - H_2O) 174, ($M^{+\cdot}$ - CH_3) 177, ($M^{+\cdot}$ - CO) 164.

4.3.1.3. 2-exo,3-endo-Dicarbomethoxy-5-endo,6-endo-O-isopropylidenenorbornane (257).-



To a stirred solution of the hydroxy lactone (256) (5.78 g, 27.26 mmole) in anhydrous 1,4-dioxane (40 ml), was added 2,2-dimethoxypropane (14.17 g, 136.4 mmole) followed by the addition of a saturated solution of hydrochloric acid in methanol (1 ml). The resultant solution was stirred at room temperature under a nitrogen atmosphere for 20 h. The solvent was evaporated in vacuo to afford a pale reddish oil which crystallised on standing and was recrystallised from ethyl acetate/light petroleum b.p. 60-80° to give 2-exo, 3-endo-dicarbomethoxy-5-endo, 6-endo-O-isopropylidenenorbornane (257) (7.05 g, 24.82 mmole, 90.9%) as a white crystal m.p. 86-87°. Found: C, 59.20; H, 7.25. $C_{14}H_{20}O_6$ requires C, 59.14; H, 5.09%.

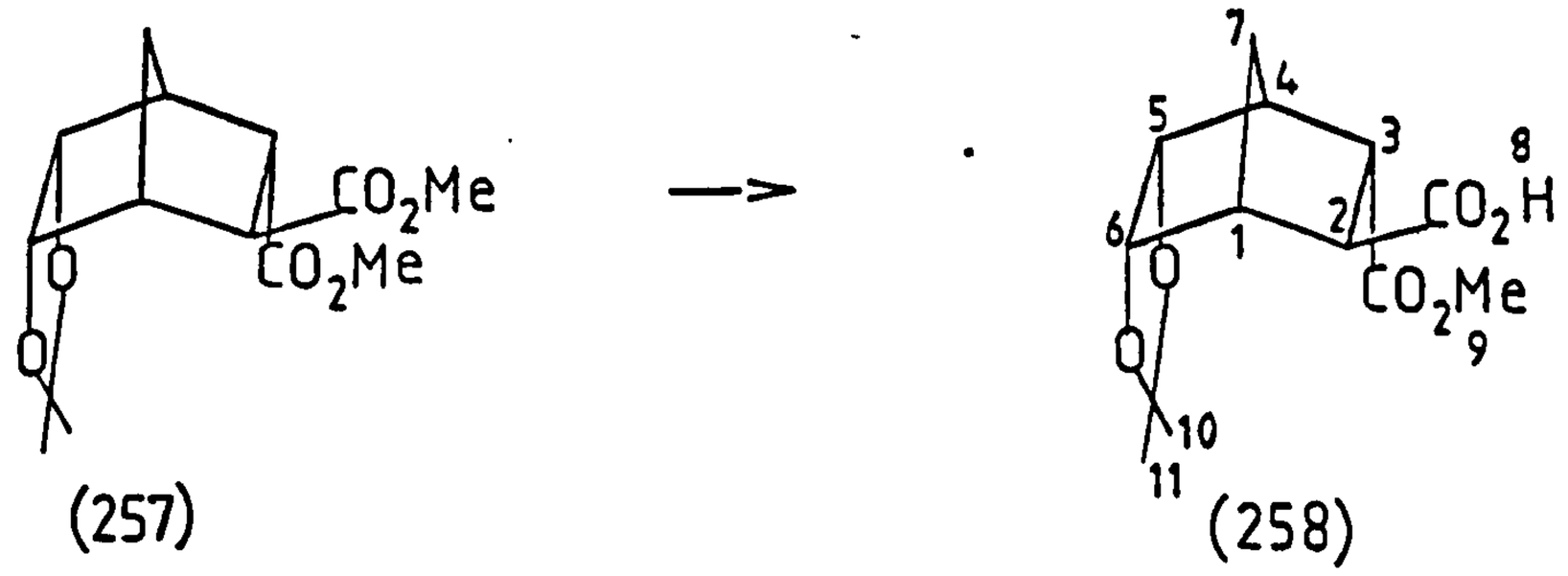
νmax cm^{-1} ($CHCl_3$) 1730 (s, C = O);

δ(90 MHz, $CDCl_3$) 4.44 (t, H-5exo, H-6exo), 3.72 (s, H-8), 3.66 (s, H-9), 3.54 (dd, H-2endo), 3.23 (q, H-3exo), 2.97 (m, H-4), 2.66 (m, H-1), 1.72 (dxt, H-7anti), 1.56 (dxq, H-7syn), 1.45 (s, H-10), 1.30 (s, H-11);

J(Hz) (5-exo, 6-exo) 4, (5-exo, 4) 5, (2-endo, 3-exd) 6, (2-endo, 7-syn) 2, (3-exo, 4) 4, (7-anti, 7-syn) 11, (7-anti, 1) 2 (7-anti, 4) 2, (7-syn, 1) 2, (7-syn, 4) 2;

$M^{+\cdot}$ 284, ($M^{+\cdot}$ - CH_3) 269, ($M^{+\cdot}$ - $2CH_3$) 254, ($M^{+\cdot}$ - CH_3COCH_3) 226.

4.3.1.4. 3-endo-Carbomethoxy-5-endo, 6-endo-O-isopropylidene norbornane-2-exo-carboxylic acid (258)



(257) (258)

Potassium hydroxide (1.63 g, 29.11 mmole) was dissolved in a (10:1) mixture of t-butyl alcohol and water (110 ml). To this stirred solution was added the diester (257) (6.34 g, 22.32 mmole) and the mixture was stirred at room temperature for 17 h when a pale yellow solution was formed. The solution was neutralised with the addition of Dowex 50W-X8 (H^+) ion exchange resin to pH = 3, the resin was filtered, washed with methanol (30 ml) and the combined filtrates were evaporated to afford a white solid. The solid was dissolved in chloroform (70 ml)

and the resultant chloroform solution was then extracted with 0.5 N aqueous sodium hydrogen carbornate (5 x 40 ml). The combined alkaline solutions were acidified to pH = 3 and extracted again with chloroform (5 x 40 ml), the combined chloroform extracts were washed with water (2 x 40 ml), dried ($MgSO_4$) and the solvent evaporated to afford 3-endo-carbomethoxy-5-endo, 6-endo-O-isopropylidene norbornane-2-exo-carboxylic acid (258) (4.5 g, 16.67 mmole, 74.7%) as white crystals, m.p. 193-194°. (Lit.[142] m.p. 193-194).

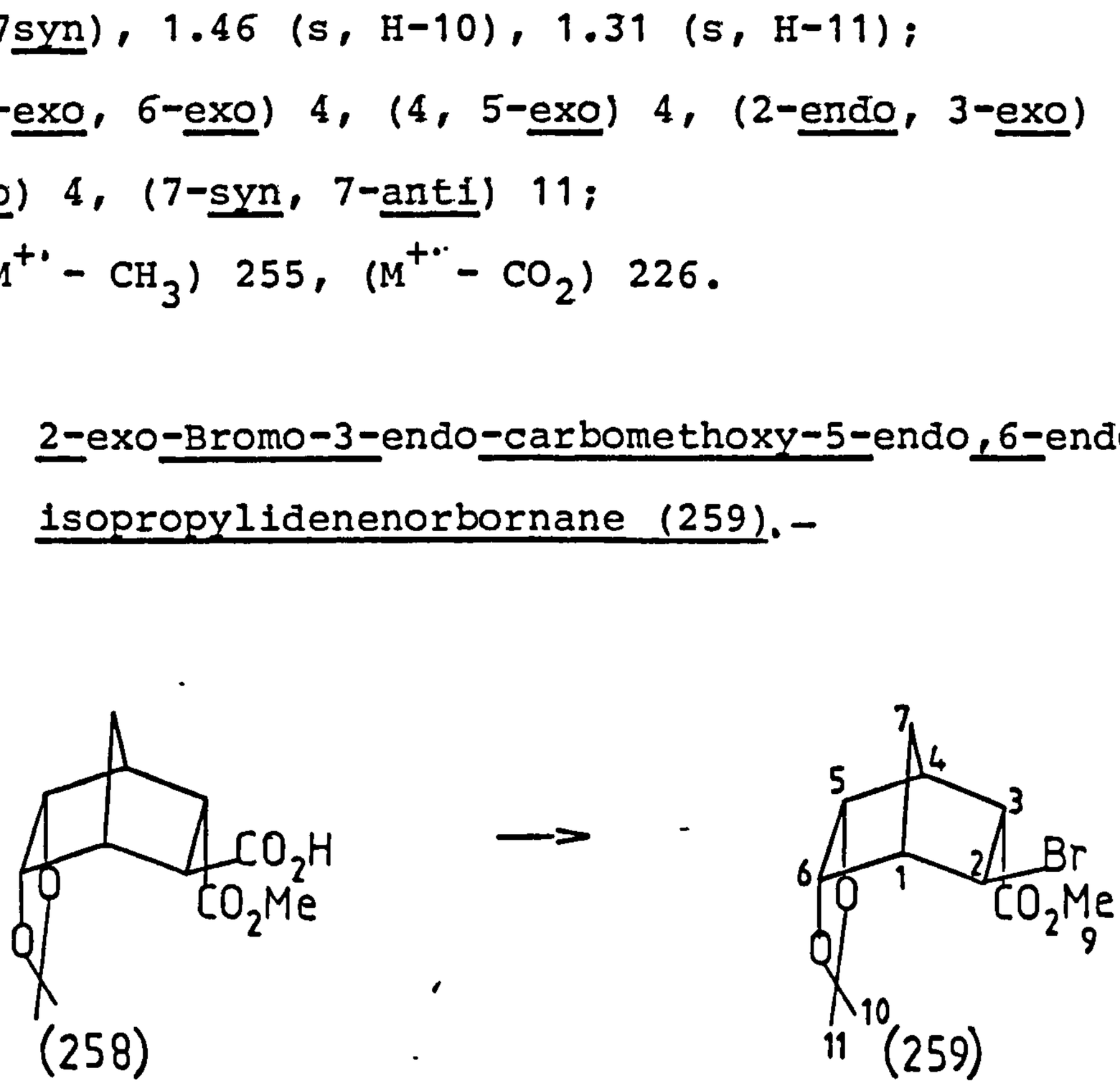
νmax cm^{-1} ($CHCl_3$) 3200 (m, COOH), 1735 (s, C = O), 1710 (s, C = O);

δ(90 MHz, $CDCl_3$) 9.22 (brs, H-8), 4.47 (t, H-5exo, H-6exo), 3.68 (s, H-9), 3.58 (brd, H-2endo), 3.23 (q, H-3exo), 2.98 (m, H-4), 2.75 (m, H-1), 1.79 (brd, H-7anti, 1.57 (brd, H-7syn), 1.46 (s, H-10), 1.31 (s, H-11);

J(Hz) (5-exo, 6-exo) 4, (4, 5-exo) 4, (2-endo, 3-exo) 6, (4, 3-exo) 4, (7-syn, 7-anti) 11;

$M^{+\cdot}$ 270 ($M^{+\cdot}$ - CH_3) 255, ($M^{+\cdot}$ - CO_2) 226.

4.3.1.5. 2-exo-Bromo-3-endo-carbomethoxy-5-endo,6-endo-O-isopropylidenenorbornane (259).-



To a well stirred solution of acid (258) (3.20 g, 11.85 mmole) in carborn tetrachloride A.R. (230 ml) was added mercuric oxide red (2.12 g, 9.79 mmole) in the dark under the nitrogen atmosphere. The mixture then was heated at reflux (oil bath temperature 95°) for 45 min, and bromine (3.20 g, 20 mmole) was added dropwise for a period of 1.5 h. After the addition was completed, the mixture was stirred and heated for a further 45 min, cooled to room temperature for a further 1 h and filtered through celite. The filtrate was washed with 0.5 aqueous sodium hydrogen carbornate (2 x 50 ml), 1 M aqueous sodium thiosulphate (2 x 50 ml), water (50 ml), dried ($MgSO_4$) and the solvent evaporated to afford 2-exo-bromo-3-endo-carbomethoxy-5-endo,6-endo-O-isopropylidenenorbornane (259) (3.42 g, 11.21 mmole, 94.74%) as a white crystal, m.p. 73-75° (Lit.[142] m.p. 75°)

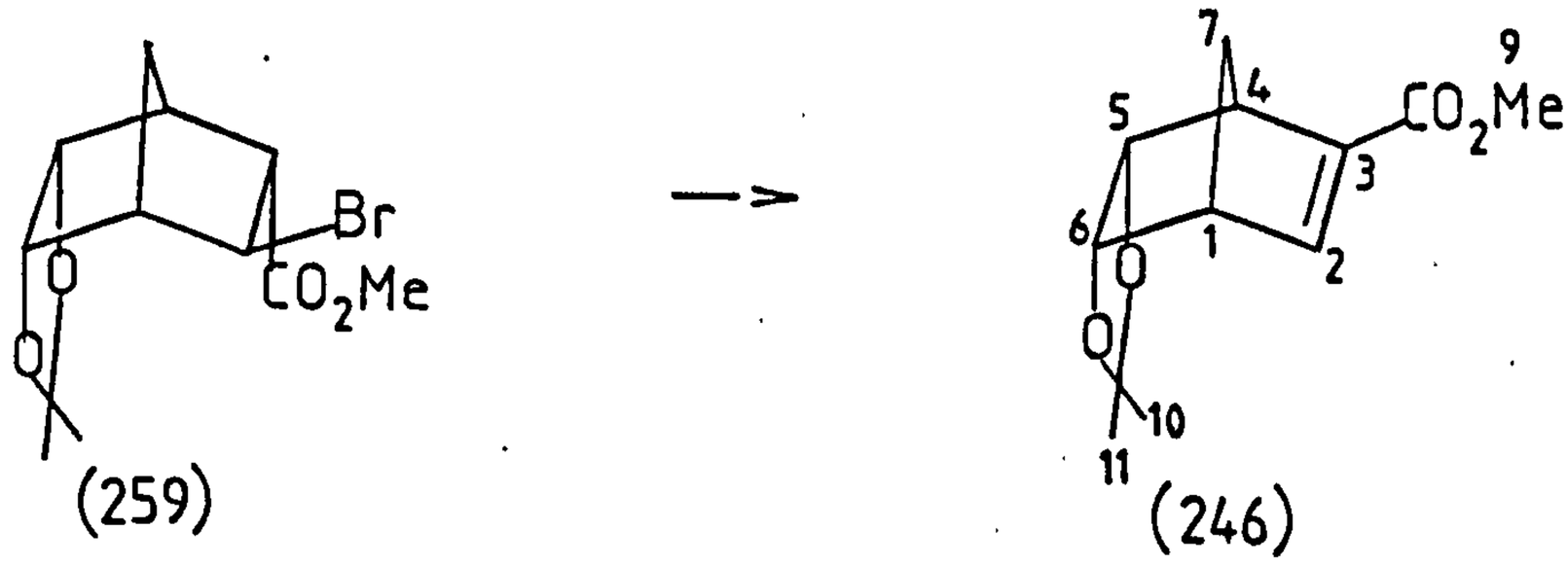
νmax cm^{-1} ($CHCl_3$) 1735 (s, C = O);

δ(90 MHz, $CDCl_3$) 4.90 (q, H-2endo), 4.48 (t, H-5exo, H-6exo), 3.70 (s, H-9), 3.18 (q, H-3exo), 2.98 (m, H-4), 2.72 (m, H-1), 2.16 (dxt, H-7anti), 1.72 (dxq, H-7syn), 1.43 (s, H-10), 1.27 (s, H-11);

J(Hz) (2-endo, 3-exo) 6, (2-endo, 7-syn) 7, (5-exo, 6-exo) 4, (5-exo, 4) 4, (3-exo, 4) 4, (7-anti, 7-syn)12, (6-exo, 1) 4;

$M^{+\cdot}$ 305, ($M^{+\cdot}$ - CH_3) 290, ($M^{+\cdot}$ - HBr) 224.

4.3.1.6. 3-Carbomethoxy-5-endo, 6-endo-O-isopropylidene norborn-2-ene (246) .—



To a solution of bromo-ester (259) (3.50 g, 11.47 mmole) in anhydrous tetrahydrofuran (50 ml) was added triethylamine (6.0 g, 59.30 mmole). The solution was then stirred and heated at reflux for 24 h, during which time a brownish white precipitate gradually formed and the solution assumed a dark colouration. The precipitate was filtered through celite, washed with tetrahydrofuran (20 ml) and the combined filtrates were evaporated to afford a dark brownish oil. Separation by column chromatography [80 g of Silica gel Merck H Type 60] with dichloromethane as eluent gave 3-carbomethoxy-5-endo,6-endo-O-isopropylidenenorborn-2-ene (246) (1.98 g, 8.8 mmole, 77.04%) as a pale yellow oil, which solidified on standing, m.p. 37-40°.

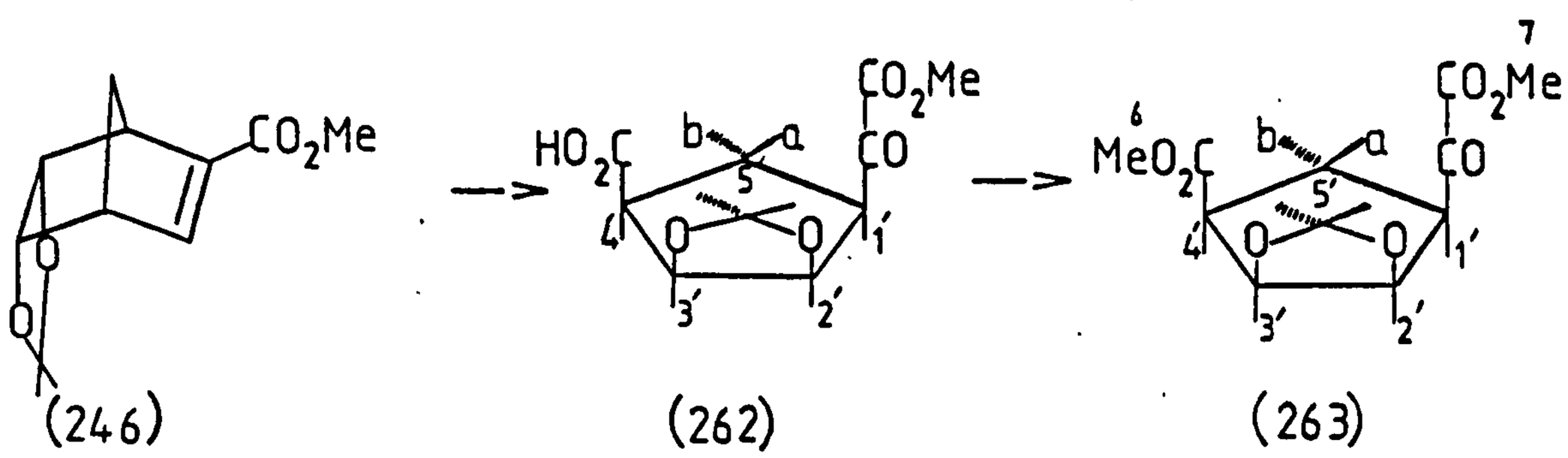
Found: C, 63.95; H, 7.05. $C_{12}H_{16}O_4$ requires C, 64.2, H, 719%.

νmax cm^{-1} ($CHCl_3$) 1730 (s, C = O);

δ(60 MHz, $CDCl_3$) 7.04 (d, H-2), 4.78 (t, H-5exo, H-6exo), 3.70 (s, H-9), 3.34 (m, H-4), 3.15 (m, H-1), 1.82 (dxt, H-7syn), 1.52 (brd, H-7anti), 1.22 (s, H-10), 1.17 (s, H-11);

J(Hz), (2, 1) 3, (5-exo, 6-exo) 3, (7-anti, 7-syn) 11; $M^{+\cdot}$ 224, ($M^{+\cdot}$ - CH_3) 209, ($M^{+\cdot}$ - CO) 196, ($M^{+\cdot}$ - CH_3COCH_3) 166.

4.3.1.7. Methyl-2-(4'β-Carbomethoxy-2'β-3'β-O-isopropylidenecyclopent-1'β-yl)glyoxylate (263).—

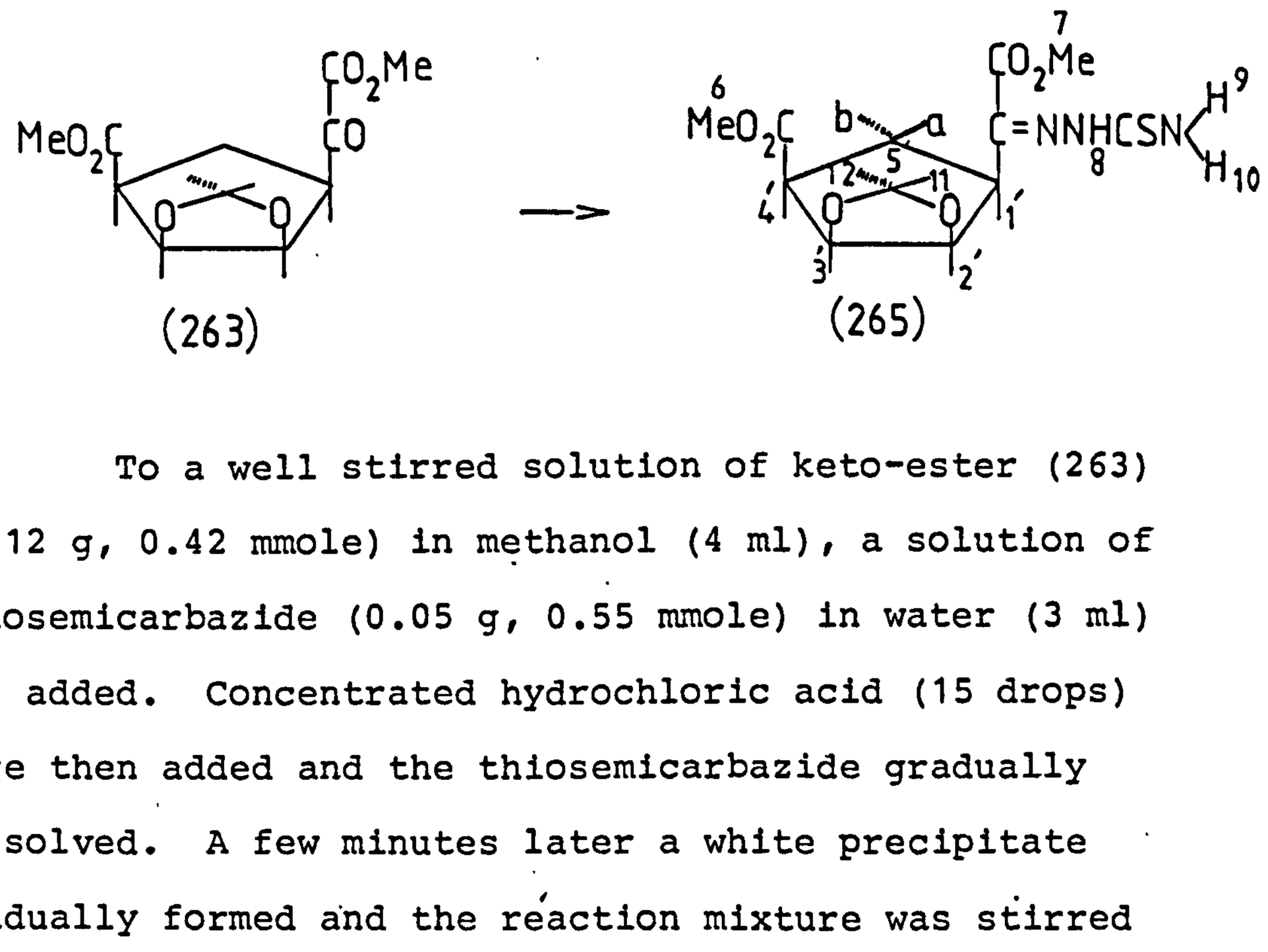


To a well stirred mixture of sodium periodate (2.11 g, 9.87 mmole) and potassium permanganate (0.19 g, 1.20 mmole) in water (60 ml) was added a solution of unsaturated ester (246) (0.395 g, 1.76 mmole) in acetone (20 ml). The resultant mixture was stirred at room temperature for 16 h, and then filtered through celite. The precipitate was washed with chloroform (20 ml) and the combined filtrates were extracted with chloroform (4 x 30 ml); the combined chloroform extracts were washed with water (2 x 30 ml), dried ($MgSO_4$), and the solvent evaporated to afford the crude acid (262) (0.23 g) as a white solid. The acid (262) was methylated with diazomethane as in 4.1.1.11 to give a pale yellow solid which on purification by column chromatography (25 g of Silica gel Merck H Type 60) with 1:3 ethyl acetate/light petroleum b.p. 60-80° as eluent afforded Methyl 2-(4'β-carbomethoxy-2'β,3'β-O-isopropylidene-cyclopent-1'β-yl)glyoxylate (263) (0.22 g, 0.77 mmole)

as a white crystalline solid, m.p. 131-133°.
Found: C, 54.35; H, 6.30. $C_{13}H_{18}O_7$ requires C, 54.54; H, 6.57%.

νmax cm^{-1} ($CHCl_3$) 1730 (s, C = O);
δ(90MHz, $CDCl_3$) 5.14 (t, H-2'), 4.88 (t, H-3'), 3.89 (s, H-7), 3.74 (s, H-6'), 3.39 (sextet, H-1'), 2.77 (sextet, H-4'), 2.50 (q, H-5'a), 1.89 (dxq, H-5'b), 1.31 (s, H-9), 1.24 (s, H-8);
J(Hz) (2',3',) 6, (2', 1') 6, (5'a, 5'b) 12, (5'a, 1') 10, (5'a, 4') 10, (5'b, 1') 6, (5'b, 4) 6;
$M^{+\cdot}$ 286, ($M^{+\cdot}$ - CH_3) 271, ($M^{+\cdot}$ - $2CH_3$) 256, ($M^{+\cdot}$ - CH_3COCH_3) 228.

4.3.1.8. Methyl-2-(4'β-Carbomethoxy-2'β-O-isopropylidene-cyclopent-1'β-yl)glyoxylate thiosemicarbazone (265).

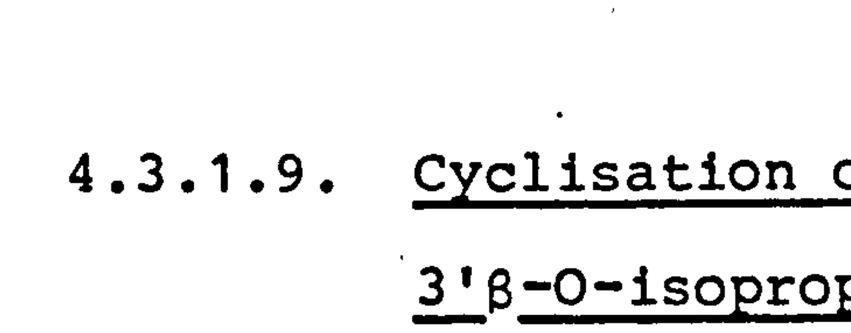


To a well stirred solution of keto-ester (263) (0.12 g, 0.42 mmole) in methanol (4 ml), a solution of thiosemicarbazide (0.05 g, 0.55 mmole) in water (3 ml) was added. Concentrated hydrochloric acid (15 drops) were then added and the thiosemicarbazide gradually dissolved. A few minutes later a white precipitate gradually formed and the reaction mixture was stirred at room temperature for a further 3 h. The precipitate

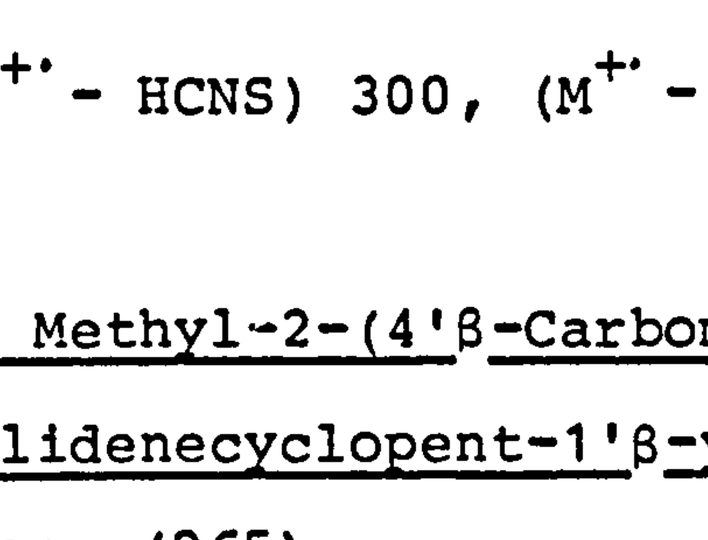
was filtered, washed with water (5 ml), methanol (5 ml) and dried to give Methyl-2-(4'β-carbomethoxy-2'β-3'β-O-isopropylidenecyclopent-1'β-yl)glyoxylate thiosemicarbazone (265) (0.12 g, 0.33 mmole, 80%) as a white crystalline solid, m.p. 207-209°, on recrystallisation from ethyl acetate/light petroleum b.p. 60-80°. Found: C, 46.59; H, 5.70; N, 11.61. $C_{14}H_{21}O_6N_3S$ requires C, 46.80; H, 589; N, 11.70%.

νmax cm^{-1} ($CHCl_3$) 3300, 3200 (m, NH), 1725 (s, C = O);
δ(90 MHz,$CDCl_3$) 12.24 (brs, H-8), 7.37 (brs, H-9), 6.61 (brs, H-10), 4.80 (q, H-2', H-3'), 3.90 (s, H-7), 3.75 (s, H-6'), 3.10 (m, H-1'), 2.80 (m, H-4'), 2.47 (q, H-5'a), 1.88 (sextet, H-5'b), 1.31 (s, H-12'), 1.25 (s, H-11');
J(Hz) (2',3') 6, (2',1') 6, (3',4') 6, (5'a, 5'b) 12, (5'b,1') 6, (5'b, 4') 6;
$M^{+\cdot}$ 359, ($M^{+\cdot}$-CH_3) 344, ($M^{+\cdot}$ - HCNS) 300, ($M^{+\cdot}$ - HN-$NHCSNH_2$) 269.

4.3.1.9. Cyclisation of Methyl-2-(4'β-Carbomethoxy-2'β-3'β-O-isopropylidenecyclopent-1'β-yl)glyoxylate thiosemicarbazone (265).—



(265)



(266)

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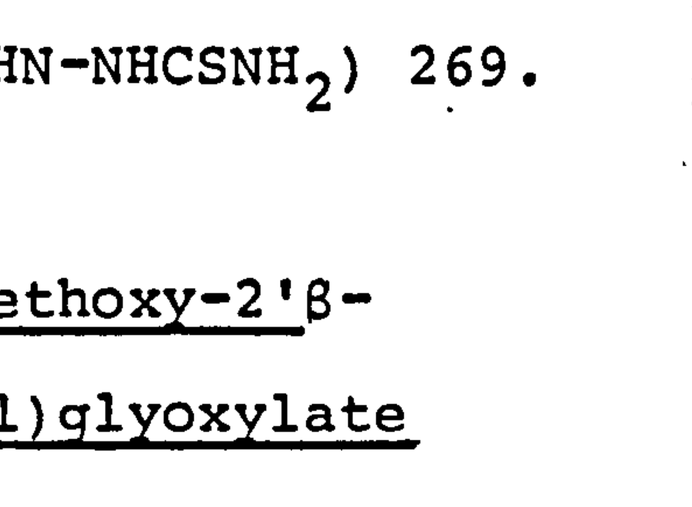


(267)

To a stirred solution of thiosemicarbazone (265) (1.38 g, 3.8 mmole) in anhydrous methanol (60 ml) was added a solution (14 ml) of 0.8 M sodium methoxide in anhydrous methanol. The solution became yellow in colour immediately after addition, and was then heated in an oil bath at 45° for 45 min. The solution was cooled and then neutralised by the addition of Dowex 50W-X8 (H^+) ion exchange resin to pH=5. The resin was filtered and the solvent evaporated to give a yellow solid (1.02 g). Purification by the column chromatography (40 g of Silica gel Merck H Type 60) with 1:1 ethyl acetate/light petroleum b.p. 60-80° as an eluent gave the following compounds:

(i) 6-(4'β-Carbomethoxy-2'β-3'β-O-isopropylidene-cyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (266) (0.323 g, 0.987 mmole) R_F = 0.35, as a white crystalline solid, m.p. 215-218°.

νmax cm^{-1} ($CHCl_3$) 3400 (m, NH), 1720 (s, C = O);
δ(60 MHz, Acetone-d_6) 12.30 (brs, NH), 11.6 (brs, NH), 5.0 (overlapping t, H-2', H-3'), 3.65 (s, H-6'), 3.0 (m, H-1', H-4'), 2.30 (m, H-5'a, H-5'b), 1.28 (s, H-8'), 1.22 (s, H-7');
u.v. λmax (EtOH) 271 nm (log ε4.29);
$M^{+\cdot}$ 327, ($M^{+\cdot}$ - CH_3) 312, ($M^{+\cdot}$ - SH) 294, ($M^{+\cdot}$ - HCNS) 268.

(ii) 6-(4'α-Carbomethoxy-2'β,3'β-O-isopropylidene-cyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (267) (0.2860 g, 0.87 mmole) R_F = 0.50 as a white crystalline solid, m.p. 185-188°.

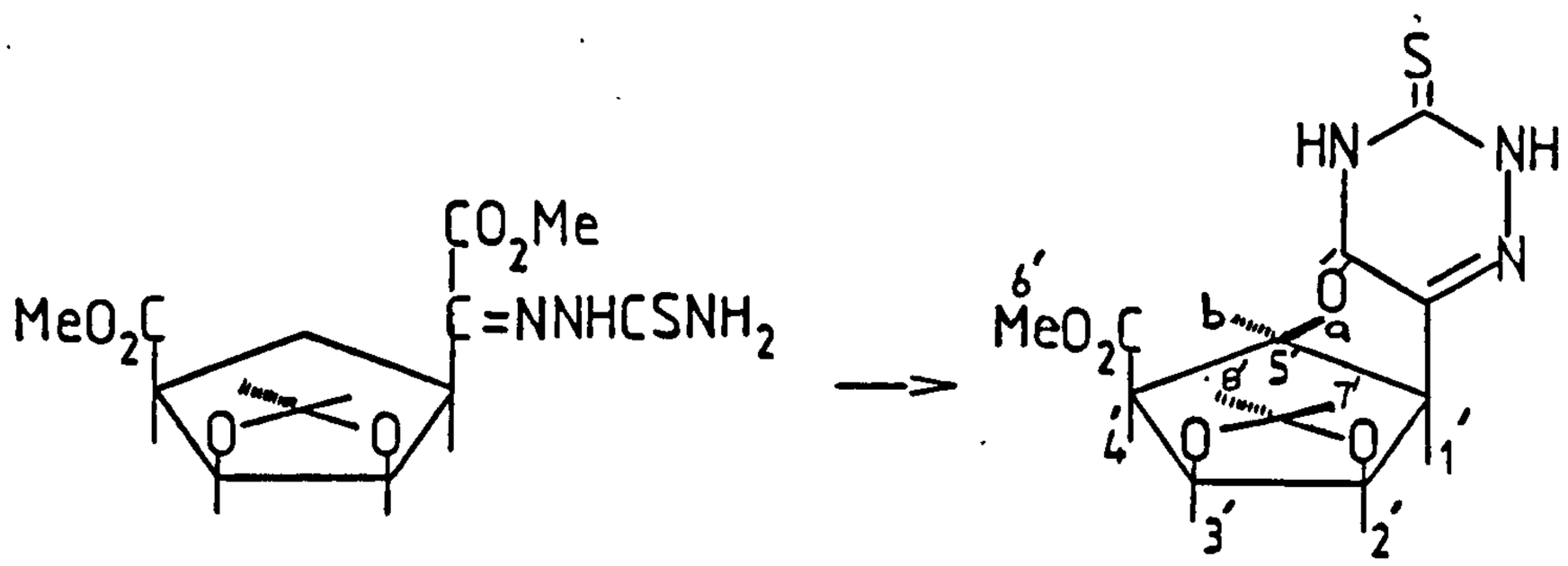
δ(90 MHz, Acetone-d_6) 11.2 (brs, NH), 4.98 (quintet, H-2', H-3'), 3.68 (s, H-6'), 3.45 (m, H-1', H-4'), 2.80 (q, H-5'a), 2.40 (dxq, H-5'b), 1.29 (s, H-8'), 1.23 (s, H-7');

J(Hz) (2',1') 5, (2', 3') 5, (5'a, 5'b) 12;

U.V. λmax (EtOH) 271 nm (logε 4.30);

$M^{+\cdot}$ 327 ($M^{+\cdot}$ - CH_3) 312, ($M^{+\cdot}$ - SH) 294, ($M^{+\cdot}$ - HCNHS) 268.

4.3.1.10. 6-(4'β-Carbomethoxy-2'β-3'β-O-isopropylidene-cyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydo-1,2,4-triazine-5-one (266).-



To a stirred solution of thiosemicarbazone (265) (0.70 g, 1.95 mmole) in anhydrous methanol (20 ml) was added 0.8 M sodium methoxide in methanol (2.5 ml). The resultant yellow solution was stirred at room temperature, and by following the reaction with t.l.c. (1:1 ethyl acetate/light petroleum b.p. 60-80°) the starting material of thiosemicarbazone (265) at R_F = 0.25 had completely reacted after 0.5 h. The solution was neutralised by the addition of Dowex 50W-X8 (H^+) to pH = 5, the resin

filtered and the solvent evaporated to give a pale yellow solid which on recrystallisation from benzene-hexane afforded 6-(4'β-carbomethoxy-2'β-3'β-O-isopropylidene-cyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (266) (0.50 g, 1.53 mmole, 78.13%) as a white crystalline solid, m.p. 215-218°.

Found: C, 47.51; H, 5.54; N, 12.43. $C_{13}H_{17}O_5N_3S$ requires C, 47.71; H, 5.19; N, 12.84%.

νmax cm^{-1} ($CHCl_3$) 3400 (m, NH), 1720 (s, C = O);

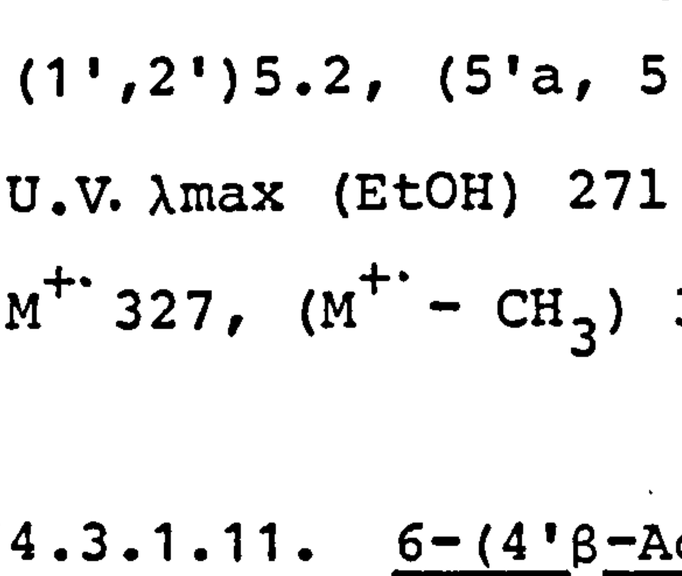
δ(250 MHz, Acetone-d_6) 5.06 (t, H-2'), 4.96 (t, H-3'), 3.24 (sextet, H-1'), 3.67 (s, H-6'), 3.08 (brs, NH), 3.02 (sextet, H-4'), 2.50 (q, H-5'a), 1.84 (sextet, H-5'b), 1.26 (s, H-7'), 1.21 (s, H-8');

J(Hz) (2',3') 5.2, (1',5'a) 12.5, (1',5'b) 12.5, (1',2')5.2, (5'a, 5'b) 12.5, (5'b,4') 12.5, (5'a,4') 12.5;

U.V. λmax (EtOH) 271 nm (logε = 4.29);

$M^{+\cdot}$ 327, ($M^{+\cdot}$ - CH_3) 312; ($M^{+\cdot}$ - SH) 294, ($M^{+\cdot}$ - HCNS) 268.

4.3.1.11. 6-(4'β-Acetoxymethyl-2'β-3'β-O-isopropylidene-cyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (268). —



(266)

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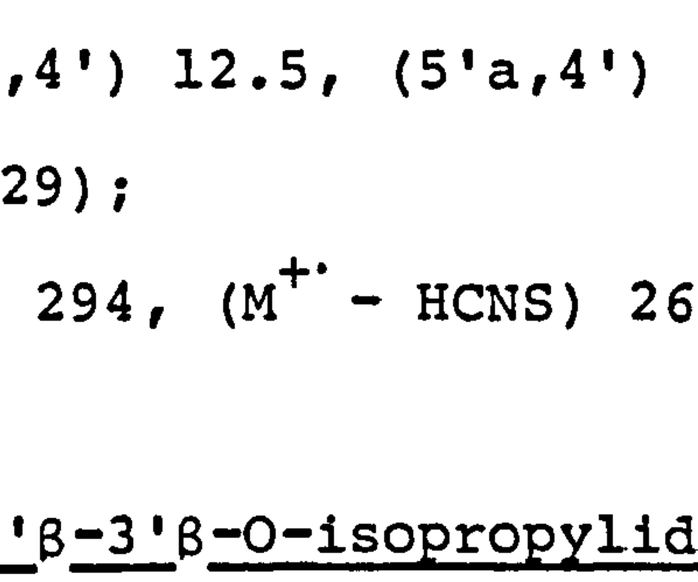


(268)

To a stirred solution of the ester (266) (0.2285 g, 0.69 mmole) in anhydrous THF (20 ml) cooled in an ice-bath under a nitrogen atmosphere, a solution of 0.5 M lithium aluminum hydride in THF (3 ml) was added. A vigorous reaction immediately occurred and the mixture was stirred for a further 0.5 h in the ice-bath and 2 h at room temperature. Ether (30 ml) and THF (20 ml) were added to the reaction mixture followed by the dropwise addition of a saturated solution of ammonium chloride until a granular precipitate formed. The precipitate was filtered, washed with THF (20 ml), and the solvent evaporated to give a pale yellow solid. The solid product was dissolved in pyridine (10 ml) and acetic anhydride (3 ml) was added and the solution stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure to afford a yellow solid which was purified by column chromatography, [20 g of Silica gel Merck H Type 60] with 9:11 ethyl acetate/light petroleum b.p. 60-80^{o} as an eluent to give 6-(4'β-acetoxy-methyl-2'β-3'β-O-isopropylidenecyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (268) (0.18 g, 0.53 mmole, 78.2%) R_F = 0.43 as white crystals m.p. 202-205^{o}.

Found: C, 49.23; H, 5.59; N, 11.95. $C_{14}H_{19}O_5N_3S$ requires C, 49.27; H, 5.57; N, 12.32%.

νmax cm^{-1} ($CHCl_3$) 3400 (m, NH), 1730 (s, C = O); δ(90 MHz, Acetone-d_6) 12.2 (brs, NH), 5.04 (t, H-2'), 4.73 (t, H-3'), 4.20 (d, H-6'), 3.25 (quintet, H-1'), 2.20 (m, H-5'a, H-4'), 2.01 (s, H-7'), 1.80 (m, H-5'b),

1.28 (s, H-8'), 1.22 (s, H-9');

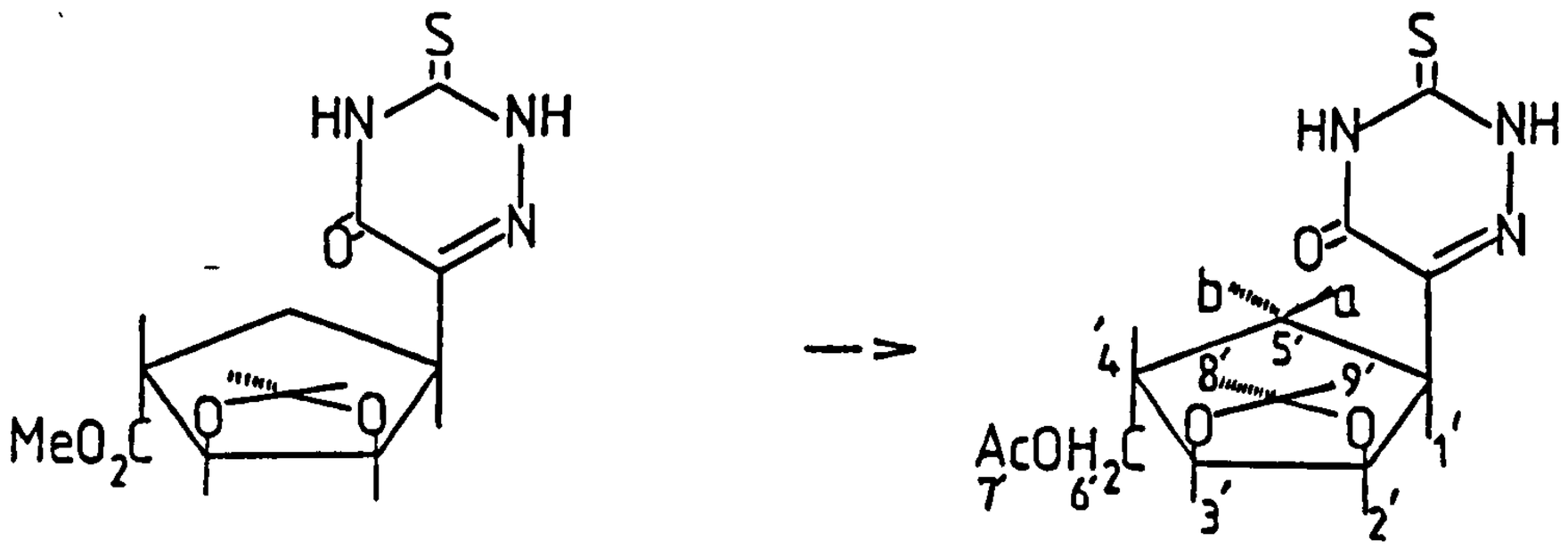
J(Hz) (2',3') 6, (2',1') 6, (6',4') 7, (1',5'a) 12,

(1',5'b) 6; (3',4')6;

u.v. λmax (CH_3OH) 271 nm (logε = 4.02);

$M^{+\cdot}$ 341, ($M^{+\cdot}$ - CH_3) 326, ($M^{+\cdot}$ - CH_3COCH_3) 283, $(C_5H_6N_3OS)^{+\cdot}$ 156.

4.3.1.12. 6-(4'α-Acetoxymethyl-2'β-3'β-O-isopropylidene-cyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (269).



(267) (269)

To a stirred solution of the ester (267) (0.23 g, 0.7 mmole) in THF (20 ml), cooled in an ice-bath under the nitrogen atmosphere, was added a solution of 0.5 M lithium aluminum hydride in THF (4 ml). Vigorous reaction immediately occurred and the mixture was stirred for a further 0.5 h in the ice-bath and 0.75 h at room temperature. The product was worked up as in 4.3.1.10 to give a yellow solid which on purification by column chromatography (20 g of Silica gel Merck H Type 60) with 2:3 ethyl acetate/light petroleum b.p. 60-80° as eluent afforded 6-(4'α-acetoxymethyl-2'β-3'β-O-isopropylidenecyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (269) (0.175 g, 0.51 mmole, 72.9%)

as white crystals m.p. 165-168°.

Found: C, 49.07; H, 5.60; N, 11.92%. $C_{14}H_{19}O_5N_3S$ requires C, 49.27; H, 5.57; N, 12.32%

νmax cm^{-1} ($CHCl_3$) 3400 (m, NH), 1730 (s, C = O), 1660 (m, C = N);

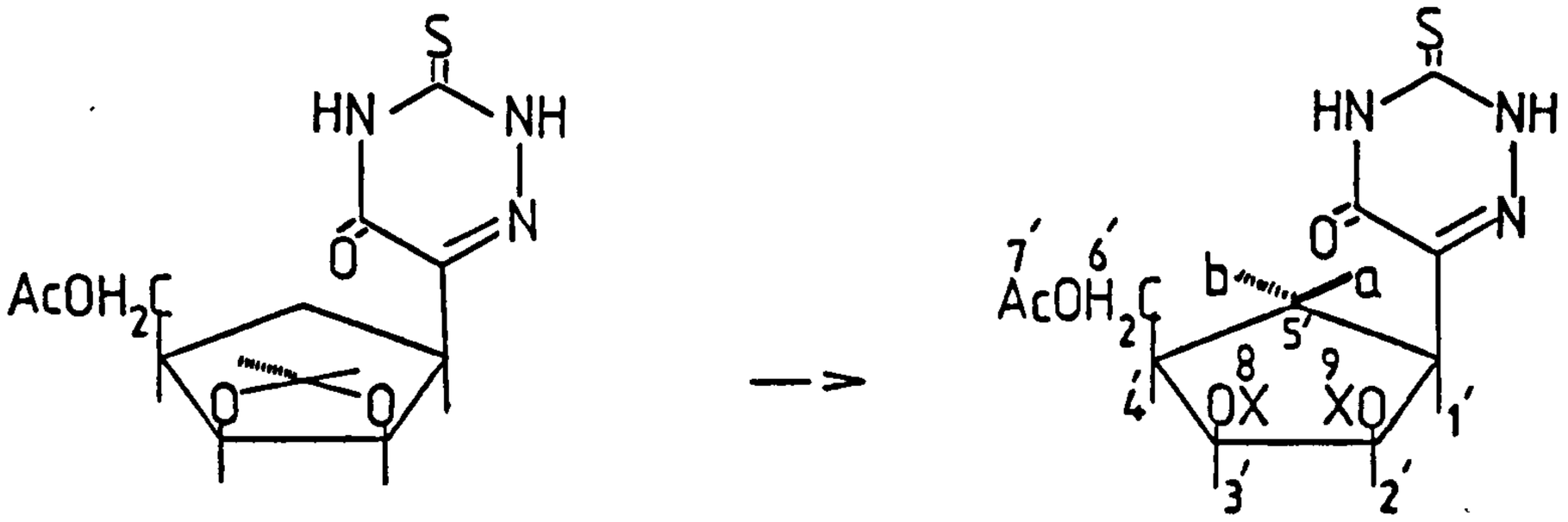
δ(90 MHz, Acetone-d_6) 11.2 (brs, NH), 5.05 (t, H-2'), 4.59 (d, H-3'), 4.0 (d, H-6'), 3.36 (quintet, H-1'), 2.50 (m, H-4', H-5'a), 2.04 (s, H-7'), 1.80 (m, H-5'b), 1.28 (s, H-8'), 1.23 (s, H-9');

J(Hz) (2',1') 5, (2',3') 5, (6',4') 6, (1',5'a) 12, (1',5'b) 6;

u.v. λmax (CH_3OH) 271 nm (logε 4.17);

$M^{+\cdot}$ 341, ($M^{+\cdot}$ - CH_3) 326, ($M^{+\cdot}$ - CH_3COCH_3) 283, $(C_5H_6N_3OS)^{+\cdot}$ 156.

4.3.1.12. 6-(4'β-Acetoxymethyl-2'β-3'β-diformyloxy-cyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (270).—



(268) (270) X = HCO

A mixture of the acetate (268) (0.25 g, 0.73 mmole) and formic acid A.R (98-100%) (15 ml) was stirred at room temperature for 48 h. The resultant homogenous solution, after the solvent was evaporated gave a yellow

oil of 6-(4'β-acetoxymethyl-2'β-3'β-diformyloxycyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (270) (0.18 g, 0.50 mmole, 69.2%).

νmax cm^{-1} ($CHCl_3$) 3380 (m, NH), 1720 (s, C = O), 1600 (m, C = N);

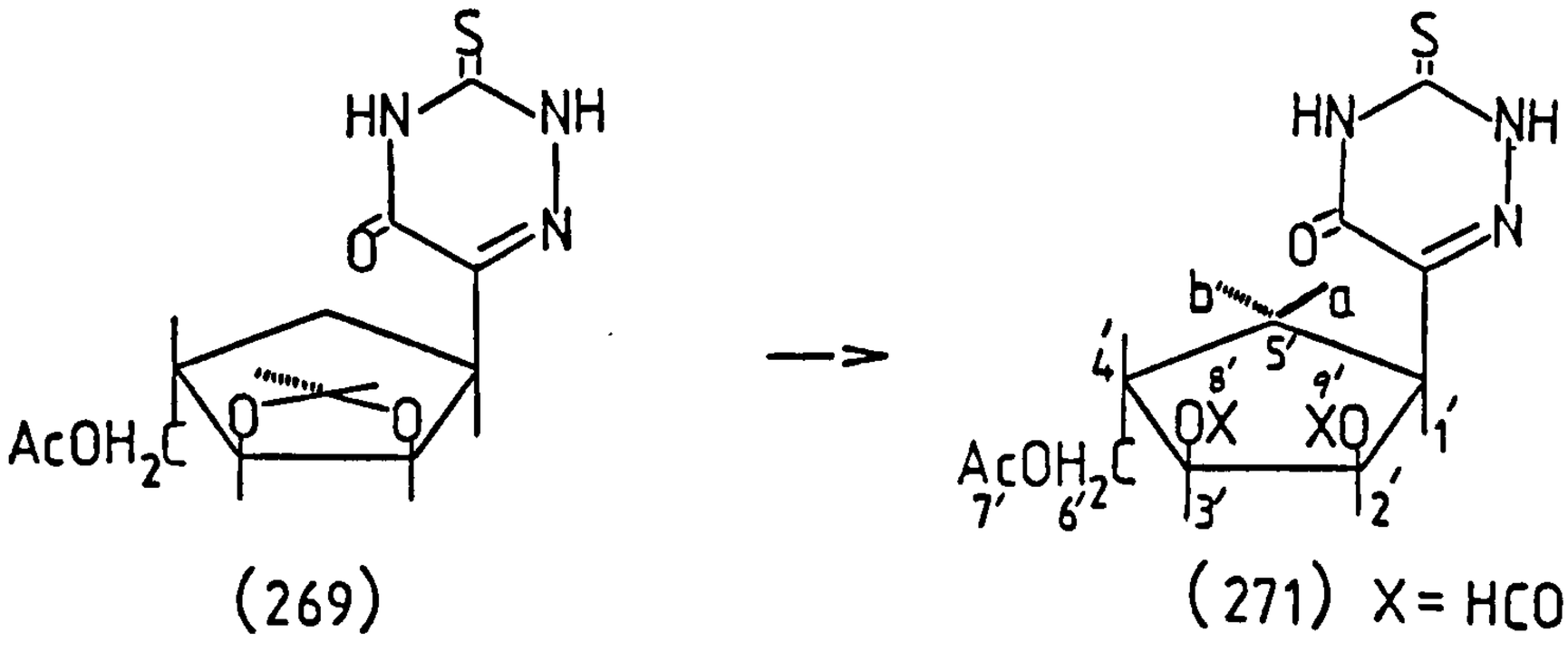
δ(60 MHz, Acetone-d_6) 8.10 (s, H-8', H-9'), 5.70 (m, H-2', H-3'), 4.20 (d, H-6'), 3.70 (m, H-1'), 2.80 (m, H-5'a), 2.30 (m, H-4', H-5'b), 2.05 (s, H-7');

J(Hz) (6',4') 7;

u.v. λmax (CH_3OH) 271 nm (logε 4.20)

$M^{+\cdot}$ 357, ($M^{+\cdot}$ - CH_3) 342, ($M^{+\cdot}$ - HCOOH) 311.

4.3.1.13. 6-(4'α-Acetoxymethyl-2'β-3'β-diformyloxy-cyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1',2,4-triazine-5-one (271). -



A mixture of the acetate (269) (9.33 mg, 0.274 mmole) and formic acid (98%) A.R. (10 ml) was stirred at room temperature for 17 h. The resultant homogenous solution, after the solvent was evaporated gave a white solid of 6-(4'α-acetoxymethyl-2'β-3'β-diformyloxycyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (271)

(85.6 mg, 0.24 mmole, 87.6%).

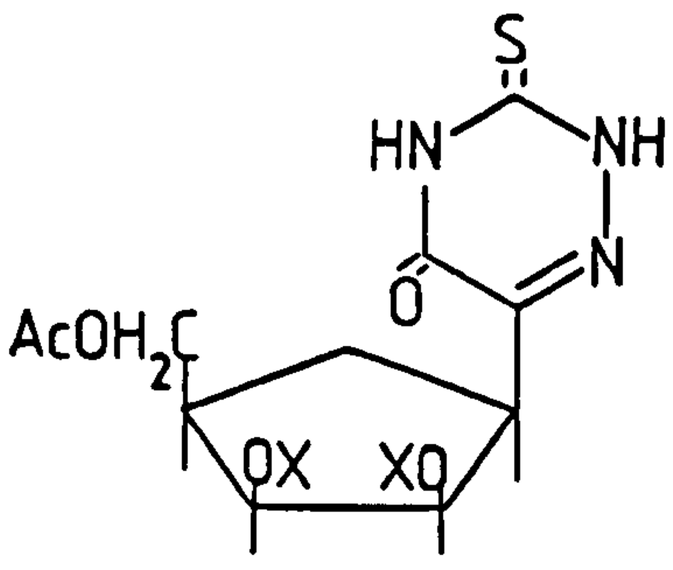
νmax cm^{-1} ($CHCl_3$) 3380 (m, NH), 1720 (s, C = O), 1600 (m, C = N);

δ(60 MHz, Acetone-d_6) 8.10 (2s, H-8', H-9'), 5.70 (t, H-2'), 5.30 (q, H-3'), 4.20 (d, H-6'), 3.8 (m, H-1'), 2.90 (m, H-4', H-5'a, H-5'b), 2.08 (s, H-7');

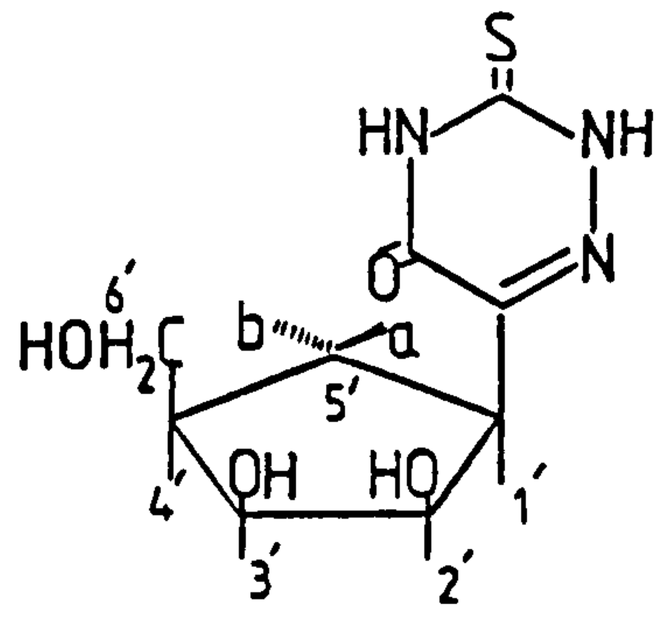
J(Hz), (2', 1') 4, (2',3') 4, (3',4') 6, (6',4') 5;

$M^{+\cdot}$ 357, ($M^{+\cdot}$ - CH_3) 342, ($M^{+\cdot}$ - HCOOH) 311).

4.3.1.14. 6-(4'β-Hydroxymethyl-2'β-3'β-dihydroxycylopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (272).—



(270) X = HCO



(272)

To a stirred solution of formate (270) (0.18 g, 0.5 mmole) in methanol (13 ml) was added 1.0 N aqueous sodium hydroxide (2.5 ml). The solution was stirred at room temperature for 16 h and was then neutralised by the addition of Dowex 50W-X8(H^+) to pH = 4. The resin was filtered and washed with methanol (20 ml), and the combined filtrates evaporated to afford a semi-solid product. Separation by column chromatography (15 g, Silica gel

Merck H Type 60) with 1:9 methanol/chloroform gave 6-(4'β-hydroxymethyl-2'β-3'β-dihydroxycyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (272) (0.1 g, 0.37mmole, 76.92%) as a white crystalline solid, m.p. 210-213°. Found: C, 40.95; H, 5.22; N, 15.40. $C_9H_{13}N_3O_4S$ requires C, 41.69; H, 5.02; N, 16.22%.

νmax cm^{-1} (Nujol) 3400 (m, NH, OH), 1680 (s, C = O), 1600 (m, C = N);

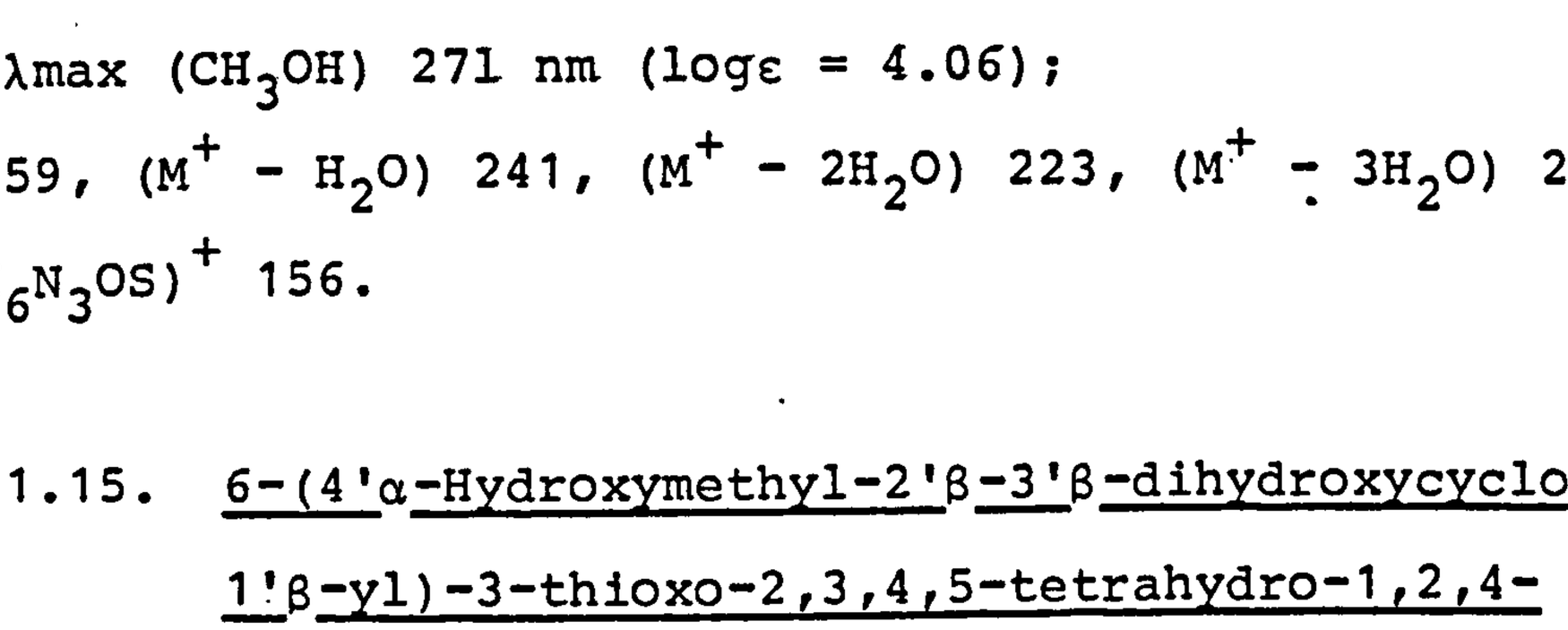
δ(250 MHz, Pyridine-d_5) 7.5 (brs, NH, OH), 5.11 (t, H-2'), 4.73 (q, H-3'), 4.27 (d, H-6'), 3.74 (dxq, H-1'), 2.95 (sextet, H-5'a), 2.60 (m, H-4'), 2.10 (sextet, H-5'b);

J(Hz) (2',1') 5, (2',3') 5, (3',4') 7.5, (6',4') 5, (1',5'a) 10, (5'a, 5'b) 15, (5'a, 4') 10, (5'b, 1) 8.8, (5'b,4) 8.8;

u.v. λmax (CH_3OH) 271 nm (logε = 4.06);

M^+ 259, ($M^+ - H_2O$) 241, ($M^+ - 2H_2O$) 223, ($M^+ - 3H_2O$) 205, $(C_5H_6N_3OS)^+$ 156.

4.3.1.15. 6-(4'α-Hydroxymethyl-2'β-3'β-dihydroxycyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (273).-



(271) X = HCO

(273)

To a stirred solution of the formate (271) (80 mg, 0.22 mmole) in methanol (15 ml) was added 1.0 N aqueous sodium hydroxide (2 ml). The resultant solution was stirred at room temperature for 16 h and worked up as in 4.3.1.14. to afford 6-(4'α-hydroxymethyl-2'β-3'β-dihydroxycyclopent-1'β-yl)-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (273) (58.0 mg, 0.22 mmole, 93%) as a white crystalline solid, m.p. 220-223° on recrystallisation from methanol/chloroform.

Found: C, 40.90; H, 5.29; N, 15.41. $C_9H_{13}N_3O_5S$ requires C, 41.69; H, 5.02; N, 16.22%.

νmax cm^{-1} (Nujol) 3400 (m, NH,OH), 1680 (s, C = O), 1600 (m, C = N);

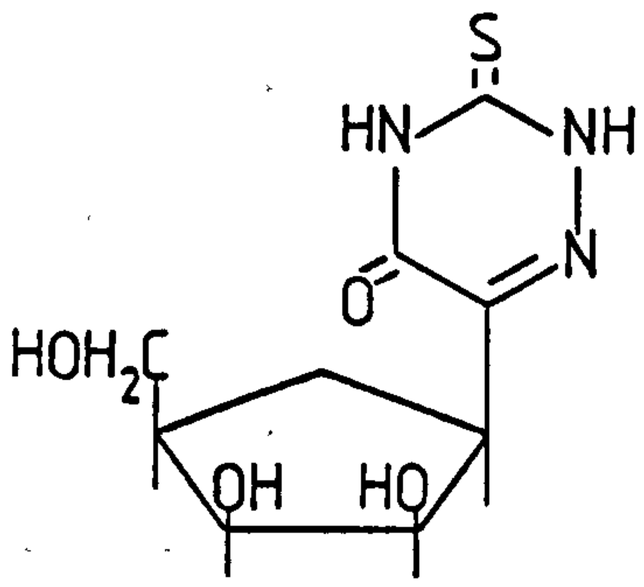
δ(250 MHz, Pyridine-d_5) 5.25 (t, H-2'), 4.60 (q, H-3'), 4.24 (dxq, H-6'a, H-6'b), 3.90 (sextet, H-1'), 3.30 (sextet, H-5'a), 2.95 (dxq, H-4'), 2.15 (dxq, H-5'b);

J(Hz) (2',1') 4.2, (2',3') 4.2, (3',4') 8.4, (6'a, 6'b) 10, (6'a, 4') 6, (6'b, 4') 4.2, (1',5a) 10, (1',5'b) 10, (5'a, 5'b) 14, (5'b, 4') 6.7;

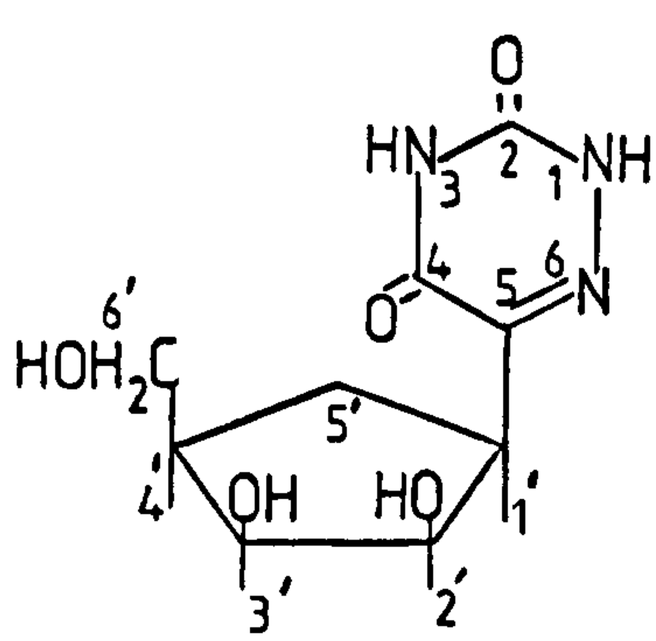
u.v. λmax (CH_3OH) 271 nm (logε 4.25);

($M^{+\cdot}$ - H_2O) 241, ($M^{+\cdot}$ - $2H_2O$) 223, ($M^{+\cdot}$ - $3H_2O$) 205, ($C_5H_6N_3OS$) 156.

4.3.1.16. Attempted Preparation of 5-(4'β-Hydroxymethyl-2'β-3'β-dihydroxycyclopent-1'β-yl)-6-azauracil (274). –



(272)



(274)

(i) A mixture of the thioxo compound (272) (50.0 mg, 0.193 mmole) in water (10 ml) and methyl iodide (0.1 ml) was heated in an oil bath at 50-55° for 6 h by the method of Bobek[160]. The excess of methyl iodide was allowed to evaporate under atmospheric pressure at 55° by removing the condenser. To the remaining solution was neutralised by addition of Dowex 1 - X8(OH). The resin was filtered, and the filtrate was then heated at 100° with Dowex 50W - X8(H^+) for 1 h. The resin was filtered and water evaporated to afford semi-solid residue. The residue was purified by column chromatography (Silica gel Merck H Type 60) with methanol as eluent gave a pale yellow semi-solid product (11.0 mg).

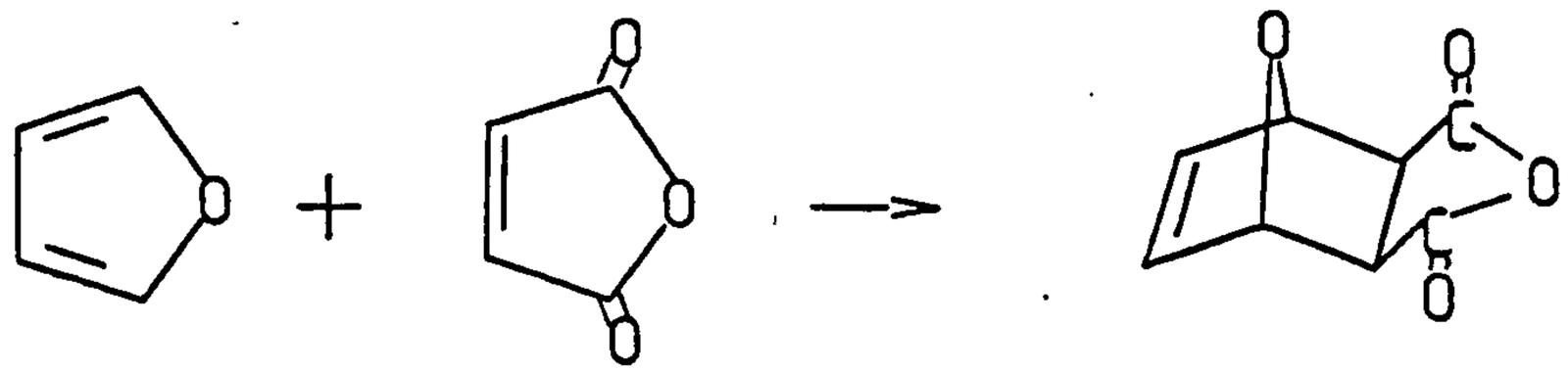
u.v. λmax (CH_3OH) 267 nm (log ε = 3.68);

mass spectrum: 215, 155, 145, 127, 113.

(ii) A mixture of the thioxo compound (272) (50.0 mg, 0.193 mmole) in water (10 ml) and methyl iodide (0.1 ml)

was heated and then the excess of methyl iodide was removed as in method (i). The remaining solution was heated at 100° for 1 h, cooled and was then run through column (2 x 15 cm) packed with Dowex 1 - X8 (Formate) and eluted with water. The solvent was evaporated to give a semi-solid product which was purified by column chromatography (Silica gel Merck H Type 60) with methanol as eluent afforded a pale viscous oil (9.3 mg) which contained 6-azauracil (274); u.v. λmax (CH_3OH) 266 nm (logε 3.70); mass spectrum 225, 224 ($M^{+\cdot} - H_2O$), 196 ($M^{+\cdot} - CO - H_2O$), 170.

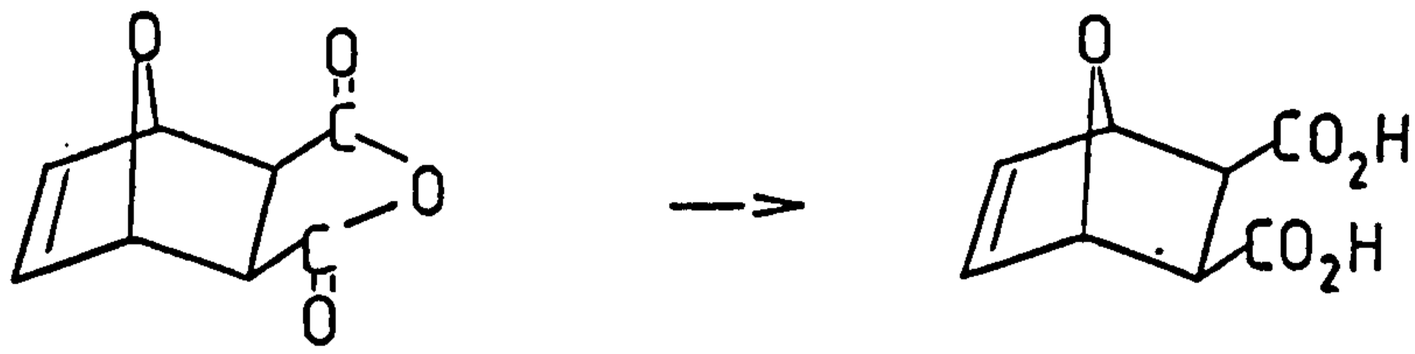
4.3.2.1. 7-oxa-Bicyclo [2.2.1] hept-5-ene-2-exo,3-exo-yldicarboxylic acid anhydride (275).-



(275)

The anhydride (275) was prepared from maleic anhydride (14.40 g, 0.15 mmole) in ether (110 ml) and furan (10.0 g, 0.15 mole) by the method of Stockmann;[183] yield (10.2 g, 0.06, 41%) as a white crystalline solid, m.p. 125°. (Lit.[183] m.p. 125°).

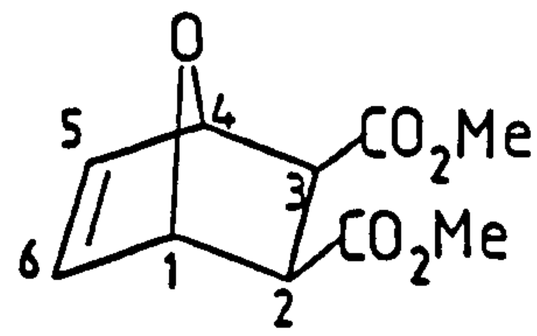
4.3.2.2. 7-oxa-Bicyclo [2.2.1] hept-5-ene-2-exo,3-exo-yldicarboxylic acid (276).-



(275) (276)

The exo, cis-acid (276) was prepared from the anhydride (275) (3.0 g, 0.018 mole) and water (35 ml) by the method of Jolivet;[184] yield (2.7 g, 0.015 mole, 81.3%) as a white crystalline solid, m.p. 132°-134°. (Lit.[184] m.p. 134°).

4.3.2.3. 7-oxa-2-exo,3-exo-Dicarbomethoxybicyclo [2.2.1] hept-5-ene (277).-



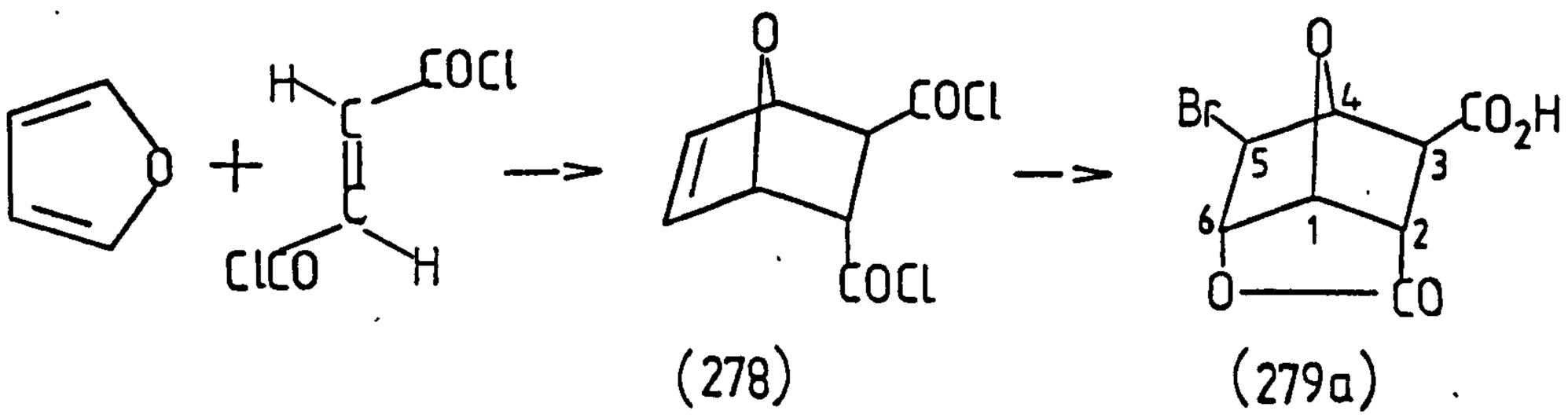
(276) (277)

A mixture of the acid (92) (1.0 g, 5.43 mmole) in ether (70 ml) was methylated with diazomethane as in 4.1.1.11, to afford the ester (277) (0.83 g, 3.92 mmole, 72.2%) as white crystals, m.p. 118-120°. (Lit.[184] m.p. 119°).

νmax cm^{-1} ($CHCl_3$) 1735 (s, C = O);

δ(60 MHz, $CDCl_3$) 6.45 (m, H-5, H-6), 5.23 (brs, H-1, H-4), 3.68 (s, OCH_3), 2.82 (brs, H-2, H-3);

4.3.2.4. 6-endo-Hydroxy-5-exo-bromo-7-oxa-3-exo-carboxybicyclo[2.2.1]hept-2-endo-ylcarboxylic acid γ-lactone (279a).-



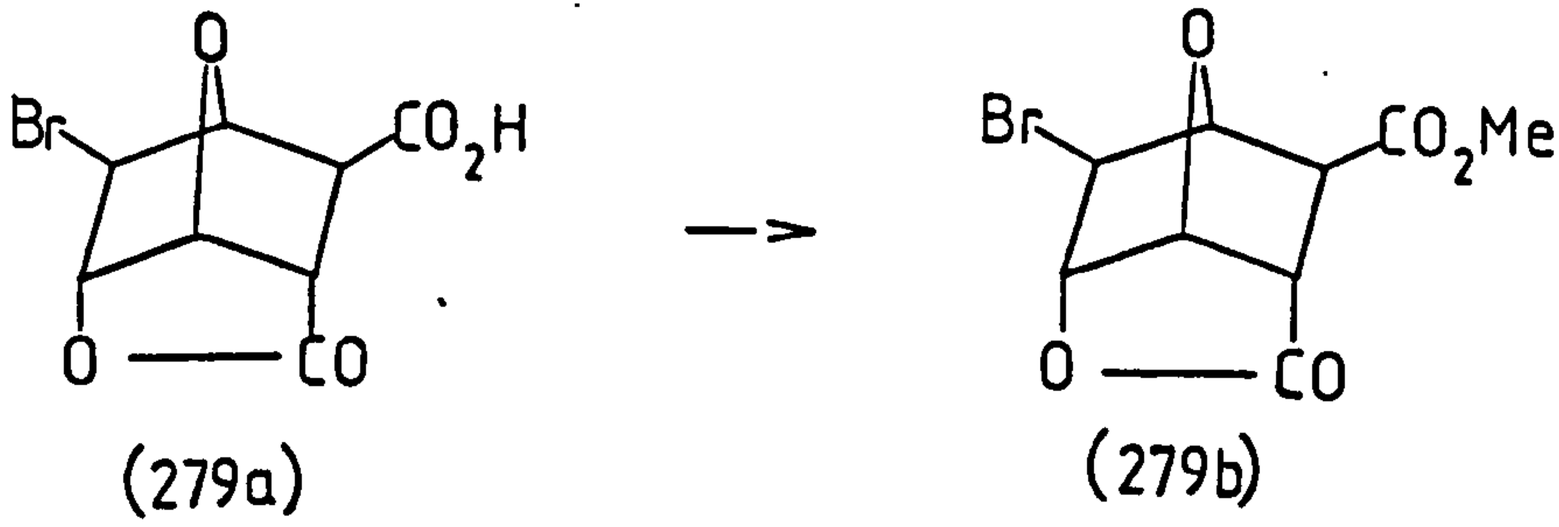
(278) (279a)

A mixture of fumaryl chloride,[185] (5.0 g, 32.7 mmole) and furan (4.0 g, 58.8 mmole) was stirred at room temperature for 24 h. Water (30 ml) was added, followed by the addition of 1 N aqueous sodium hydroxide until homogenous solution obtained (30 ml). The solution was cooled at 0^{o} and bromine was added slowly as in the method of Berson and Swindler[186] to afford the bromo γ-lactone (279a) (3.2 g, 12.16 mmole, 37.2%) as a white crystalline solid, m.p. 235-237°. (Lit.[186] m.p. 236-238°).

νmax cm^{-1} (Nujol) 3400 (m, COOH), 1800 (s, C = O of γ-lactone), 1710 (s, C = O of acid);

δ(90 MHz, Acetone-d_6) 5.60 (t, H-1), 5.09 (brs, H-4), 5.0 (brd, H-6exo), 4.35 (s, H-5endo), 3.42 (d, H-3endo), 3.23 (q, H-2exo); J(Hz) (1,6-exo) 5, (1, 2-exo) 5, (2-exo, 3-endo) 2.

4.3.2.5. 6-endo-Hydroxy-5-exo-bromo-7-oxa-3-exo-carbomethoxybicyclo [2.2.1.] hept-2-endo-ylcarboxylic acid γ-lactone (279b).—



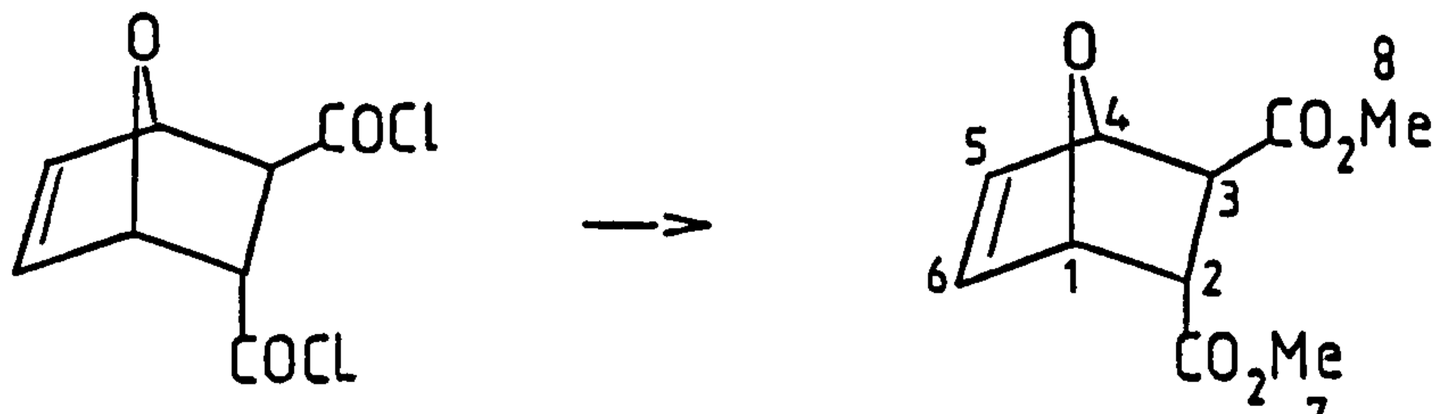
Concentrated sulphuric acid (1 ml) was added to a solution of the acid γ-lactone (279a) (0.3 g, 1.14 mmole) in methanol (50 ml). The resultant solution was slowly stirred and heated at reflux for 3 h, cooled and the solution was concentrated to (10 ml) by evaporation under reduced pressure. Chloroform (50 ml) was added to the residue and the resultant solution was washed with 0.5 N aqueous sodium hydrogen carbornate (2 x 20 ml), water (20 ml), dried ($MgSO_4$) and the solvent evaporated to afford white crystals of ester γ-lactone (279b) (0.25 g, 0.9 mmole, 79.4%), m.p. 169-172°. (Lit.[186] m.p. 170-171°).

νmax cm^{-1} ($CHCl_3$) 1800 (s, C = O),1740 (s, C = O);

δ(60 MHz, $CDCl_3$) 5.50 (t, H-1), 5.13 (brs, H-4), 5.0 (d, H-6exo), 3.97 (s, H-5endo), 3.80 (s, OMe), 3.40 (brd, H-2exo), 3.12 (brs, H-3endo);

J(Hz) (1,6-exo) 6, (1,2-exo) 5·

4.3.2.6. 7-oxa-2-endo, 3-exo-Dicarbomethoxybicyclo [2.2.1] hept-5-ene (280).-



(278) (280)

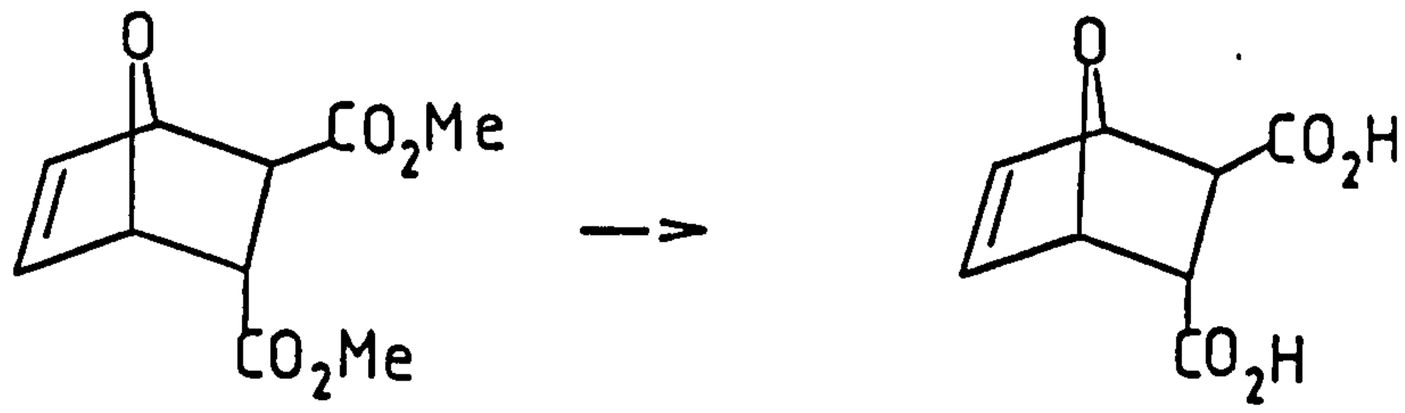
A mixture of fumaryl chloride (2.6 g, 0.015 mole) and furan (3.13 g, 0.05 mole) was stirred at room temperature for 24 h. Methanol was then slowly added to the product mixture of adduct (278) and unchanged fumaryl chloride. The resultant solution was stirred at room temperature for 40 min and then the solvent evaporated to afford a white solid. Separation by column chromatography [80.0 g of Silica gel Merck H Type 60] with 3:7 ethyl acetate/light petroleum b.p. 60-80° as an eluent gave the ester (280) (1.80 g, 8.5 mmole, 56.6%) as a white crystalline solid, m.p. 90-92°. (Lit.[187] m.p. 90-91°).

νmax cm^{-1} ($CHCl_3$) 1740 (s, C = O);

δ(60 MHz, $CDCl_3$) 6.40 (m, H-5, H-6), 5.22 (m, H-2, H-4), 3.73 (s, H-8), 3.67 (s, H-7), 3.60 (t, H-2exo), 2.84 (d, H-3endo);

J(Hz) (2-exo, 1) 5, (2-exo, 3-endo) 5.

4.3.2.7. 7-oxa-Bicyclo [2.2.1] hept-5-ene-2-endo, 3-exo-yldicarboxylic acid (280a).-



(280) (280a)

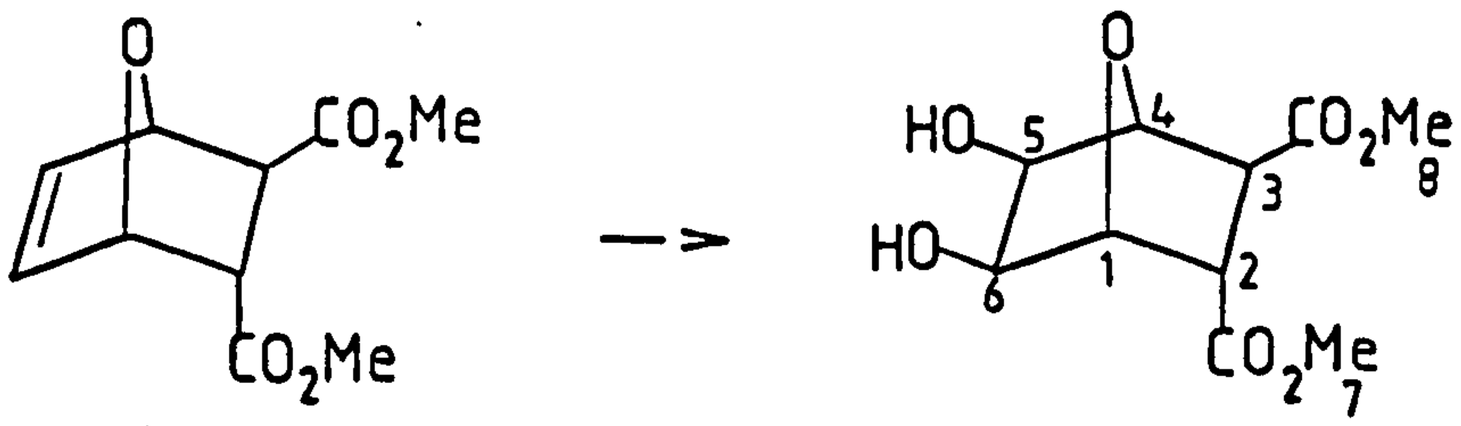
Aqueous sodium hydroxide (1 M, 20 ml) was added to a solution of the ester (280) (1.32 g, 6.22 mmole) in methanol (50 ml). The solution was stirred at room temperature for 6 h, neutralised by the addition of Dowex 50W-X8(H), the resin removed by filtration and the solvent evaporated to afford the trans-acid (280a) (0.92 g, 5 mmole, 80.7%) as a white crystalline solid (methanol) m.p. 170-172° (Lit.[187] m.p. 175°).

νmax cm^{-1} (Nujol) 3300 (m, COOH), 1710 (s, C = O);

δ(60 MHz, Acetone-d_6) 9.0 (brs, H-7, H-8), 6.50 (dxq, H-5, H-6), 5.20 (m, H-1, H-4), 3.50 (t, H-2exo), 2.75 (d, H-3endo);

J(Hz) (5,6) 6, (5,1) 2, (6,1) 2, (2-exo, 1) 5, (2-exo, 3-endo) 5.

4.3.2.8. Dimethyl-5-exo,6-exo-dihydroxy-7-oxabicyclo [2.2.1]heptane-2-endo,3-exo-dicarboxylate (281).-



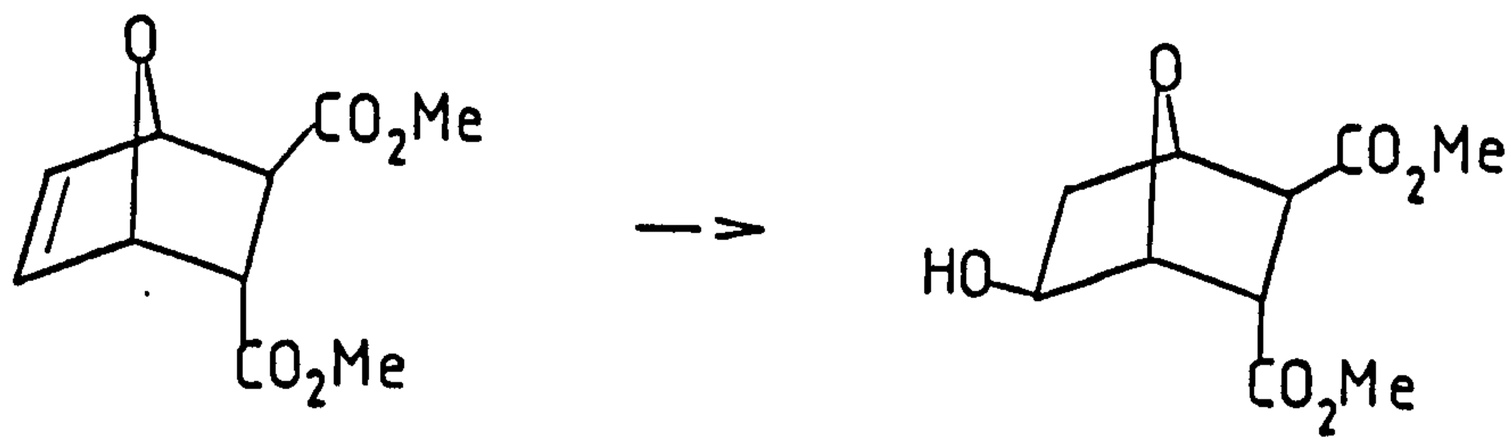
(280) (281)

To a stirred solution of the ester (280) (1.0 g, 4.7 mmole) in ethanol (60 ml) cooled at - 40° to -60° was added a solution of potassium permanganate (0.7 g, 4.42 mmole) and magnesium sulphate (0.7 g) in water (17 ml). The resultant mixture was stirred at -40° to -60° for a further 1 h, warmed to 0° and sulphure dioxide gas was then bubbled through the solution until the permanganate colour disappeared.

The precipitate of MnO_2 was filtered and the filtrate was concentrated under reduced pressure to (20 ml) and the resultant solution was extracted with chloroform (5 x 20 ml), the combined extracts were washed with water (20 ml), dried ($MgSO_4$) and the solvent evaporated to afford the diol (281) (0.6 g, 2.4 mmole, 52.2%) as a white crystalline solid, m.p. 111-113°.

νmax cm^{-1} ($CHCl_3$) 3400 (m, OH), 1740 (s, C = O);
δ(60 MHz, $CDCl_3$) 4.65 (s, H-4), 4.50 (d, H-1), 3.90 (d, H-5, H-6), 3.70 (brs, H-7, H-8), 3.60 (brs, OH), 3.45 (t, H-2exo), 3.0 (d, H-3endo);
J(Hz) (1,2-exo) 6, (2-exo, 3-endo) 6;
$M^{+\cdot}$ 246, ($M^{+\cdot}$ - H_2O) 228, ($M^{+\cdot}$ - CO) 218.

4.3.2.9. Dimethyl 6-exo-hydroxy-7-oxabicyclo[2.2.1]hept-2-endo, 3-exo-dicarboxylate (283).-



(280) (283)

To a solution of the ester (280) (0.5 g, 2.36 mmole) in THF (15 ml) cooled in an ice-bath was added 0.4 M diborone (3 ml) in THF, and the reaction mixture was then stirred for 1 h. The excess of diborane was destroyed by the addition of a few drops of water, and the resulting mixture was oxidised by the addition of 1 N aqueous sodium hydroxide (2 ml), followed by the dropwise addition of (100%) hydrogen peroxide (2 ml). The ice-bath was removed after 15 min and the reaction mixture was left stirred at room temperature for a further 1 h. The mixture was saturated with sodium chloride and the precipitate was filtered and washed with chloroform (30 ml). The combined filtrates were washed with a saturated solution of sodium chloride (2 x 20 ml), dried ($MgSO_4$) and the solvent evaporated to afford the alcohol (283) (0.42 g, 1.85 mmole, 79.2%) as a white crystalline solid, m.p. 70-72°.

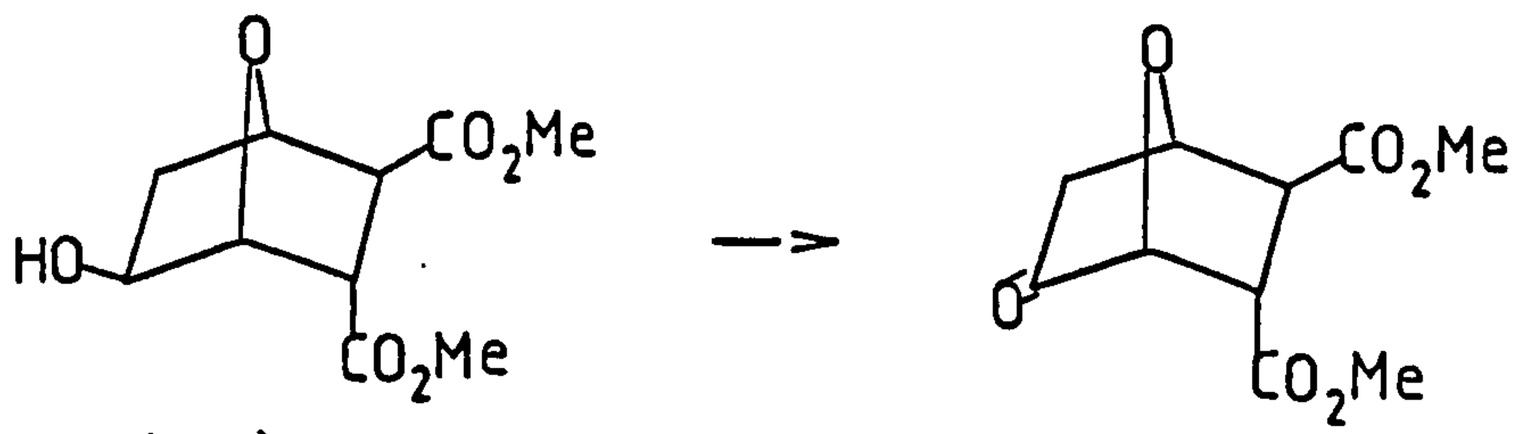
νmax cm^{-1} ($CHCl_3$) 3400 (m, OH), 1740 (s, C = O); δ(60 MHz, $CDCl_3$) 4.80 (d, H-1), 4.56 (d, H-4), 3.95 (brt, H-6), 3.70 (s, H-7, H-8), 3.40 (brt, H-2exo, OH),

2.90 (brd, H-3endo), 1.90 (m, H-5exo) H-5endo);

J(Hz) (1,2-exo) 6, (4,5-exo) 5, (2-exo, 3-endo) 5;

$M^{+\cdot}$ 230, ($M^{+\cdot}$ - H_2O) 212, ($M^{+\cdot}$ - CO_2CH_3) 171.

4.3.2.10. Dimethyl 7-oxa-bicyclo [2.2.1] heptan-6-one-2-endo, 3-exo-dicarboxylate (284).—



To a solution of the alcohol (283) (0.5 g, 2.20 mmole) in anhydrous dimethylformamide (3 ml) was added a solution of pyridinium dichromate (4.0 g, 10.8 mmole) in dimethylformamide (5 ml). The reaction mixture was stirred at room temperature for 16 h, then water (50 ml) was added and the resultant solution was extracted with chloroform (5 x 20 ml). The combined chloroform extracts were washed with water (2 x 20 ml), dried ($MgSO_4$) and the solvent evaporated to afford the ketone (284) (0.3 g, 1.3 mmole, 60.6%) as a yellow oil.

νmax cm^{-1} ($CHCl_3$) 1740 (s, C = O);

δ(60 MHz, $CDCl_3$) 5.20 (d, H-1), 4.60 (d, H-4), 3.72 (brs, H-7, H-8), 3.62 (t, H-2exo), 3.30 (d, H-3endo), 2.35 (m, H-5exo, H-5endo);

J(Hz) (1,2-exo) 5, (4,5-exó) 6, (2-exo, 3-endo) 5, (5-exo, 5-endo) 12;

$M^{+\cdot}$ 228, ($M^{+\cdot}$ - CH_3) 213, ($M^{+\cdot}$ - CO) 200.

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